

Mechanisms of endocrinology

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Mechanisms of disease: The endocrinology of obstructive sleep apnoea

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Abstract

Obstructive sleep apnoea (OSA) is a common disorder that is associated with serious co-morbidities with a negative impact on quality of life, life expectancy and health costs. As OSA is related to obesity and is associated with sleep disruption, increased inflammation and oxidative stress, it is not surprising that OSA has an impact on the secretion of multiple hormones and is implicated in the development of many endocrine conditions. On the other hand, many endocrine conditions that can affect obesity and/or upper airways anatomy and stability have been implicated in the development or worsening of OSA. This bi-directional relationship between OSA and the endocrine system has been increasingly recognised in experimental and epidemiological studies and there are an increasing number of studies examining the effects of OSA treatment on endocrine conditions and vice-versa. In this review article, we will critically appraise and describe the impact of OSA on the endocrine system including obesity, dysglycaemia, the pituitary, the thyroid, the adrenals, the reproductive system and the bones. In each section, we will assess whether a bi-directional relationship exists, and we will describe the potential underlying mechanisms. We have focused more on recent studies and randomised controlled trials where available and attempted to provide the information within clinical context and relevance.

54 Introduction:

55 Obstructive Sleep Apnoea (OSA) is a common disorder that affects 13-33% of men and 6-19% of
56 women¹. OSA is characterized by instability in the upper airways (UAs) leading to recurrent episodes
57 of the UA obstruction, particularly during the transition to sleep and rapid-eye-movement (REM)
58 sleep (characterised by low-amplitude, mixed-frequency theta EEG waves, pronounced eye activity
59 and low muscle tone²) (see online supplement)³⁻⁶. These repeated obstructions are associated with
60 recurrent episodes of oxygen desaturation/ re-saturation, cyclical changes in blood pressure (BP),
61 heart rate, sympathetic activity, and intrathoracic pressure, brief microarousals and changes to sleep
62 architecture, such as the loss of REM and slow wave sleep (SWS or deep sleep, is stage N3 of NREM
63 sleep characterised by high-amplitude slow waves, further decrease in muscle tone, possible eye
64 movement cessation and is a restorative sleep stage decreasing though with age²) (Figure 1 & online
65 supplement)^{3, 5, 7}.

66 The interactions between OSA and the endocrine system have attracted much attention and they
67 often can be bi-directional, which is not surprising considering the diurnal secretion pattern of many
68 hormones. In addition, OSA treatment (namely continuous positive airway pressure CPAP) has an
69 impact on the endocrine system (such as insulin resistance, cortisol secretion) while treating
70 endocrine disorders (such as obesity, hypothyroidism, or acromegaly) can also improve OSA.
71 Moreover, the well-established higher OSA risk in men vs. women also emphasises the potential
72 relationship between sex hormones and OSA pathogenesis. Hence, it is important to understand the
73 links between OSA and the endocrine/metabolic system in order to improve our understanding of the
74 pathogenesis and the comorbidities and mortality associated with OSA and a variety of endocrine
75 disorders⁸.

76 In this article, we will review the interactions between OSA and the endocrine system and we will
77 highlight the underlying mechanisms underpinning this bidirectional relationship when exists, as well
78 as explore the potential impact of OSA treatment on the endocrine disorders and vice versa. Some
79 aspects of this article require some understanding of the pathogenesis of OSA, hence we have
80 provided an overview of OSA and its pathogenesis in the online supplement.

81 OSA & Obesity Interplay

82 Obesity is a major risk factor for the development of OSA⁹⁻¹¹, which is driving the increase in OSA
83 prevalence^{1, 12}. Obesity prevalence in patients with OSA (approx. 70%) is also higher than that of the
84 general population¹³.

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85 **The impact of weight change on OSA**

86 Weight changes have significant impact on OSA and its severity. In a longitudinal study of randomly
87 selected patients from Wisconsin, a 10% weight gain over 4 years was associated with 32% (95%CI 20-
88 45%) increase in the **Apnoea- Hypopnoea Index (AHI: the average number of apnoea and hypopnea**
89 events per hour of sleep) and 6-fold higher risk of developing moderate to severe OSA (95%CI 2.2-17)
90 compared to weight stability¹¹. On the other hand, 10% weight loss was associated with 26% (95%CI
91 18-34%) decrease in the AHI compared to weight stability¹¹, partly due to a reduction in UAS
92 collapsibility observed with weight loss¹⁴. The favourable impact of weight loss on OSA and its
93 severity seems to be evident regardless of the method of losing weight such as life-style
94 interventions, pharmacotherapy, or bariatric surgery as has been shown by several studies among
95 them and **randomized controlled trials (RCTs)**¹⁴⁻¹⁸.

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96 In a RCT, of 60 patients with obesity and moderate to severe OSA, laparoscopic adjustable gastric
97 banding (LAGB) resulted in greater weight loss (5.1 vs. 27.8 kg), and greater reductions in AHI (based
98 on PSG) (-14.0 vs. -25.5 events/hour; between-group difference was -11.5 events/h 95% CI -28.3 to
99 5.3; P = 0.18) over 2 years compared to life-style intervention (dietary, physical activity and behavioral
100 conventional program)¹⁵. In a recent post-hoc analysis of this RCT, patients who achieved a normal
101 supine AHI (i.e. AHI < 5/h) lost significantly more weight than those who had persistently elevated AHI
102 (weight change -23.0 [-21.0 to -31.6]% vs. -6.9 [-1.9 to -17.4]%, *p* = 0.001)¹⁹. Other studies also
103 showed significant improvements in the AHI and a high proportion of OSA resolution following sleeve
104 gastrectomy and gastric bypass^{16, 17}. A meta-analysis confirmed the positive impact of bariatric
105 surgery on OSA severity, by showing a significant reduction of AHI post-surgery (by 38.2 events/hour,
106 95% CI: 31.9-44.4)²⁰. **A more recent systematic review and meta-analysis by Wong et al showed that**
107 bariatric surgery was associated with a reduction in the AHI (WMD -25.1 events/h
108 (95%CI -29.9, -20.2)); with the pooled mean pre- and post-surgery AHI of 39.3 ± 15.1 and 12.5 ± 5.6
109 events/h respectively; however OSA persisted in most patients and there was high between studies
110 heterogeneity mostly due to baseline AHIO and duration of follow up²¹. Hence, RCTs remain needed
111 to address the impact of bariatric surgery on OSA, although these might be challenging to conduct. In
112 another RCT, liraglutide 3mg daily combined with lifestyle intervention resulted in greater reductions
113 in weight (-5.7% vs -1.6%, *P*<0.0001) and AHI (-12.2 vs -6.1 events/h, estimated treatment difference:
114 -6.1 events/h; 95% CI -11.0 to -1.2, *P*=0.015) compared to life-style intervention only over 32 weeks¹⁸.
115 The degree of weight loss correlated significantly with improvements in OSA in this trial¹⁸.

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116 Obesity can affect multiple aspects of OSA pathogenesis, as summarised in **Figure 2**²²⁻³⁶.

117 The impact of OSA on weight (Figure 2B)

118 The impact of OSA on obesity is controversial. One possibility is that OSA could lead to worsening
119 obesity via multiple mechanisms such as increased excessive daytime sleepiness (EDS) leading to a
120 reduction in physical activity, sleep disruption leading to changes in hunger and satiety hormones³⁷⁻³⁹
121 (leptin resistance, increased ghrelin, increased orexin, and neuropeptide Y levels), changes to sleep
122 duration and architecture⁴⁰⁻⁴⁴. Sleep restriction was associated with increased activation of the brain
123 regions related to emotional response to stimuli and motivation and reward system based on
124 functional MRI, which was similar to what observed following energy deprivation resulting in
125 corrective behavior of seeking food^{45, 46}. This is supported by cross-sectional studies showing that the
126 AHI was significantly associated with increased preference of calorie-dense foods independent of the
127 severity of obesity in adolescents and children^{47, 48} and that visceral obesity was increased in patients
128 with OSA and short sleep duration (< 5 h/night) (OR, 4.40, 95% CI, 1.80-10.77), compared to those
129 who slept ≥ 7 h/night⁴⁹. In addition, disruption of sleep architecture (suppression of SWS as happens
130 in OSA) without affecting sleep duration in young healthy men, increased hunger for high-calorie food
131 in the afternoon and evening⁵⁰. OSA could also contribute to increased fat mass by activation of the
132 HPA axis and increased cortisol secretion and by hypercapnia induced adipogenesis ~~OSA could also~~
133 ~~cause obesity via increased cortisol secretion⁵¹ and hypercapnia induced adipogenesis⁵²~~. However,
134 despite the above mentioned plausible mechanisms, epidemiological evidence for an impact of OSA
135 on weight longitudinally is lacking. One small (n=53) prospective study of patients with newly
136 diagnosed OSA showed 7.4±1.5 kg weight-gain over 12 months, but these patients had also a history
137 of weight gain in the year preceding OSA diagnosis⁵³, hence quantifying the impact of OSA is difficult
138 without an appropriate control group.

139 Nonetheless, if OSA is a cause of obesity, then it would be expected that OSA treatment will lead to
140 weight loss. However, a systematic review of 3181 patients from 25 RCTs showed that CPAP resulted
141 in a modest but statistically significant increase in BMI and weight compared to control (BMI change:
142 -0.018±0.243 kg/m² for controls vs. 0.134±0.273 kg/m² for CPAP; weight change: -0.096±0.718 kg
143 for controls vs. 0.417±0.718 kg for CPAP)⁵⁴. The mechanisms behind the weight gain after CPAP are
144 not fully elucidated. However, CPAP reduces leptin (**satiety hormone**), intermittent hypoxia and
145 sympathetic activity leading to **reductions in lipolysis and energy expenditure** and hence can cause
146 weight gain⁵⁵⁻⁶¹.

147 Furthermore, it is plausible that OSA can lead to weight loss via increased sympathetic activity leading
148 to increased energy expenditure and lipolysis via lipoprotein lipase inhibition and sympathetic
149 activation^{62, 63}. The net effects of the above-mentioned opposing mechanisms/impacts of weight gain

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150 and weight loss is potentially weight maintenance in patients with OSA. CPAP treatment tilts the
151 balance between these opposing mechanisms towards weight gain by inhibiting sympathetic activity
152 (Figure 2), but this might be opposed to a certain degree by the impact of CPAP on increasing GH
153 levels leading to lipolysis⁶⁴. The above, however, is only a hypothesis that requires further
154 investigations. ~~It is plausible that OSA might have multifaceted effects that can promote weight gain
155 and weight loss resulting in largely opposing effects and when patients receive CPAP then the balance
156 is tilted towards weight gain (Figure 2). This is, however, a hypothesis that needs to be examined.~~

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157 OSA & Dysglycaemia

158 As obesity is a major risk factor for OSA, much of the research in this field has focused on pre-
159 diabetes/T2D. However, it is now increasingly recognized that OSA is common in patients with T1D as
160 well. In this section, we will focus mostly on pre-diabetes/T2D but we will also summarise the
161 evidence regarding T1D.

162 Epidemiology:

163 In general population studies, OSA has been shown to be associated with various comorbidities,
164 including T2D⁹, which is not surprising since obesity is a common risk factor for OSA and T2D^{7, 65}.
165 Several cross-sectional studies showed a high prevalence of OSA (mild: $5 \leq \text{AHI} < 15$; moderate: $15 \leq$
166 $\text{AHI} < 30$; severe: $\text{AHI} \geq 30$) in patients with T2D (8.5-86%, 23.8-70% moderate-to-severe OSA), and a
167 high prevalence of T2D in patients with OSA (15-30%)^{7, 66}. This variation in prevalence estimates is due
168 to different diagnostic methods and criteria used to define OSA and differences in studies
169 populations⁶⁷⁻⁷¹.

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170 Longitudinal studies have also shown that OSA is an independent risk factor for the development of
171 T2D. A recent meta-analysis of 8 studies (63,647 participants) showed that OSA was an independent
172 risk factor for T2D after adjustment for age, sex, and BMI (adjusted RR 1.49, 95% CI:1.27, 1.75), which
173 remained significant even in studies that defined OSA as $\text{AHI} \geq 5$ (adjusted RR 1.42; 95% CI 1.02,
174 1.99)⁷². A small RCT of 12 weeks in 80 patients with obesity ($\text{BMI} > 45 \text{ kg/m}^2$ and mostly with
175 metabolic syndrome) suggested that CPAP resulted in improvements in impaired glucose tolerance
176 status compared to no CPAP and that CPAP lowered the 2-h glucose levels following OGTT⁷³.
177 However, there remains a need for large RCTs of long duration to assess the impact of CPAP, on its
178 own or in combination with lifestyle intervention, on T2D prevention.

179 OSA and insulin resistance and β -cell function:

180 The impact of OSA on incident T2D is likely to be mediated by the effects of OSA on insulin resistance
181 (IR) and β -cell dysfunction⁷. Studies that examined the relationship between OSA and IR had

182 conflicting results, due to variations in the definitions of OSA and IR, but most of the studies showed
183 an association⁶⁵. The association between OSA and IR was present in lean men, suggesting that the
184 relationship is not dependant on obesity^{74, 75}. Variation in EDS might contribute to the variation in the
185 associations between IR and OSA observed in the different studies as Barcelo et al showed that the
186 association between OSA and IR was only evident in patients with EDS vs. without EDS despite being
187 matched for BMI⁷⁶. In support of the relationship between OSA and IR, a recent meta-analysis of 6
188 RCTs of adults without diabetes showed a favourable effect of CPAP on IR vs. no CPAP (mean
189 difference in HOMA-IR -0.43; 95%CI:-0.75 to -0.11, p=0.008)⁷⁷.

190 The impact of OSA on β -cell function is much less examined in the literature. In one study of patients
191 without diabetes, patients with moderate-to-severe OSA had a lower β -cell function (measured using
192 the disposition index during frequent sampling intravenous glucose tolerance test (IVGTT)) compared
193 to healthy controls; and higher AHI was associated with lower β -cell function despite adjustment for
194 obesity⁷⁸. Similar results were found in a more recent study⁷⁹ and in another study in patients with
195 T2D⁸⁰. Similar to IR, CPAP improved β -cell function in compliant patients with moderate to severe
196 OSA without diabetes (uncontrolled trial)⁸¹ or with pre-diabetes (RCT)⁸².

197 Mechanisms: OSA leading to dysglycaemia and T2D:

198 There are several putative mechanisms linking intermittent hypoxia (IH) and sleep fragmentation to
199 IR, β -cell dysfunction, and dysglycaemia³³ summarised in **Figure 3**.

200 In rodent models, IH has been shown to increase β -cell death⁸³ and impair β -cell function⁸⁴. Results
201 from experimental studies in healthy adults showed that 5 hours of IH (24.3 events/h, average oxygen
202 saturation 90.6%, range 75.4-98%) resulted in blunted, rather than increased, insulin secretion
203 despite reductions in insulin sensitivity (based on IVGTT)⁸⁵. Chronic IH-**(CIH)** can lead to β -cell
204 dysfunction and IR via increased oxidative stress⁸⁶, which pancreatic β -cells are less able to handle
205 compared to other tissues⁸⁷⁻⁸⁹, and increased inflammation (increased CD8⁺ cytotoxic T-cells
206 recruitment, shift to M1-proinflammatory macrophages in crown-like structures, IL and TNF- α)^{90, 91}. In
207 addition, chronic IH can increase free fatty acid (FFA) release leading to ectopic fat deposition in the
208 liver and muscle resulting in IR⁹⁰. The impacts of chronic IH and oxidative stress on IR could also be
209 mediated by hypoxia-inducible factor (HIF) tissue effects⁹². In rodents, 35 days of chronic IH
210 decreased insulin receptor expression and phosphorylation in skeletal muscle and adipose tissue, but
211 not in the liver which was accompanied by up-regulation of HIF-1 α in the liver and down-regulation
212 HIF-1 α and HIF-2 α in skeletal muscle⁹³.

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213 Changes in sleep architecture can also contribute to the effects of OSA on glucose metabolism⁹⁴. In an
214 experimental study of young healthy adults, all-night suppression of SWS (without awakening the
215 subjects, changing sleep duration, or REM sleep) was achieved via acoustic stimuli of varying intensity
216 and frequency for three nights⁹⁴. This resulted in a reduction in insulin sensitivity (by 25%, which is
217 similar to a weight gain of 8-13 kg) without a compensatory increase in insulin release (based on
218 IVGTT) ⁹⁴. These changes in insulin sensitivity and β -cell function were associated with increased
219 sympathetic activity and in some cases changes in cortisol levels^{94, 95}. In addition, several other
220 neurohormonal mechanisms are involved in the links between OSA and T2D, which are summarised
221 in **Figure 3** ^{30,39, 51, 65, 96-113}.

222

223 The impact of Dysglycaemia on OSA:

224 While the impact of OSA on glucose metabolism has been widely studied, the impact of T2D and
225 dysglycaemia on OSA has not received much attention. Many cross-sectional studies showed a high
226 prevalence of OSA in patients with T2D as we detailed above, but whether this prevalence is higher
227 than an age- and obesity- matched population without T2D remains unclear. Recently, a population-
228 based study of 151,194 participants with T2D showed a Hazard risk of incident OSA 1.53 (95% CI:
229 1.32-1.77) and further patients treated with insulin had higher risk of OSA, especially if they were
230 women (1.43; 95%CI: 1.11-1.83)¹¹⁴. In addition, the incidence and natural history of OSA in patients
231 with T2D are currently unknown. One longitudinal study assessed the relationship between IR and
232 possible OSA prospectively and showed that HOMA-IR was an independent predictor for incident
233 witnessed sleep apneas (not formally diagnosed OSA) over 6 years (OR: 1.31; 95%CI1.13-1.51)¹¹⁵.

234 Several possible mechanisms make it plausible that dysglycaemia/diabetes can lead to the
235 development or worsening of OSA as summarized in **Figure 3** ^{7, 11, 115-132}.

236 OSA in patients with T2D

237 OSA and glycaemic control in T2D:

238 Several cross-sectional studies in patients with T2D showed that patients with OSA had worse fasting
239 plasma glucose, glycaemic variability and HbA1c compared to patients without OSA despite
240 adjustment for confounders (difference in HbA1c between patients with and without OSA 0.7 to
241 3.7%)^{7, 133-135}. In addition, OSA severity is correlated with worse glycaemic measures⁷. Interestingly,
242 one study showed that the relationship between AHI and HbA1c was only evident for the AHI during
243 REM sleep and not during NREM sleep (after adjustment for confounders)¹³⁶. This raised the
244 possibility that OSA treatment might improve glycaemic parameters in patients with T2D.

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Several uncontrolled trials showed that CPAP improved glycaemic variability, postprandial glucose levels and HbA1c over the short-term^{65, 137}. However, 3 RCTs showed conflicting results. Two of these RCTs showed that CPAP had no impact on HbA1c^{138, 139}, while another RCT showed that CPAP for 6 months lowered HbA1c by -0.4% (95%CI: -0.7% to -0.04%; $P = 0.029$) while there was no change in HbA1c in the control group¹⁴⁰. These conflicting results could be due to differences in studies population (β -cell reserve), baseline glycaemic control (for example one of the negative RCTs had a baseline HbA1c of 7.3%, while the RCT that showed positive effects of CPAP had baseline HbA1c of 7.6%)¹³⁹, or study duration (3 vs 6 months)¹³⁸. There were no significant changes in weight or anthropometrics measures in these RCTs between the CPAP and the control arm to explain the conflicting results. However, an important difference between these RCTs was compliance with CPAP; the positive RCT showed CPAP usage of 5.2 hours per night compared to below 4 hours/night in the trial by West et al^{138, 140}. Longer CPAP duration per night might have an important impact on glycaemic control as REM tend to occur later during sleep and the AHI during REM correlated with HbA1c better than the AHI during NREM^{82, 136}. Hence, there is still a need for well-designed RCTs of longer CPAP duration to answer the question whether CPAP can (or cannot) improve glycaemic control in patients with T2D.

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OSA and vascular complications in patients with T2D:

Several plausible mechanisms have led to the hypothesis that OSA could lead to the development or progression of macro- and micro-vascular complications in patients with T2D as shown in **Figure 4**¹⁴¹⁻¹⁴⁶.

The relationship between OSA and CVD in patients with T2D has not been studied widely. A retrospective observational study showed that in patients with T2D and newly diagnosed OSA, CPAP for 9-12 months lowered systolic (mean change -6.81, 95%CI -9.94 to -3.67) and diastolic (-3.69, -5.53 to -1.85) BP¹⁴⁷. Similar reductions in BP levels were observed after 3 months of CPAP in an RCT in which patients with T2D and OSA were randomised to early (<1 week) or late (1-2 months) CPAP¹⁴⁸. The Sleep AHEAD study showed an association between AHI and a history of stroke (adjusted OR 2.57; 95% CI: 1.03, 6.42) but not with coronary artery disease¹⁴⁹. In a longitudinal study in 132 patients with T2D and a normal baseline exercise echocardiography test, OSA predicted incident coronary artery disease (adjusted HR 2.2; 95% CI: 1.2-3.9; $p = 0.01$) and heart failure (3.5; 1.4-9.0; $p < 0.01$) over a median follow-up of 4.9 years¹⁵⁰. In another recent study of 1311 patients who had percutaneous coronary intervention (PCI), OSA was associated with increased risk of major adverse cardiac and cerebrovascular events (MACCE) over 3 years in patients with diabetes mellitus (adjusted HR 2.03, 95% CI 1.10-3.74, $P = 0.023$) after adjustment for age, sex, ethnicity, BMI, and

hypertension¹⁵¹. There is no interventional RCT published regarding the impact of CPAP on CVD in patients with T2D.

OSA has been shown to be associated with diabetes-related microvascular complications including peripheral neuropathy, chronic kidney disease (CKD), retinopathy and autonomic neuropathy⁷¹. Most of these studies were cross-sectional and no interventional studies have been published although several are ongoing.

A recent systematic review of 15 cross-sectional studies concluded that there was no convincing evidence that OSA was associated with diabetic retinopathy (DR), but that there was some evidence to suggest that OSA was associated with greater DR severity¹⁵². The systematic review also suggested that OSA was associated with maculopathy¹⁵². It is plausible that the impact of OSA on DR is more related to disease progression rather than the development of disease (which is a function of hyperglycaemia)⁷. The increased retinal oxygen demands overnight will make the retina particularly vulnerable to the effects of the IH that occur in patients with T2D and OSA. This is supported by a recent longitudinal study in patients with T2D in which OSA was not associated with the development of DR but was associated with progression to pre-proliferative and proliferative DR¹⁵³. In this longitudinal study, OSA was associated with sight threatening DR (STDR) (adjusted OR 2.3; 95% CI, 1.1–4.9; P = 0.035), and maculopathy (adjusted OR 2.7, 95%CI 1.2–5.9, p= 0.01) at baseline¹⁵³. After a median follow-up of 43.0 (IQR 37.0-51.0) months, patients with OSA were more likely than patients without OSA to develop pre-proliferative/ proliferative DR (18.4% vs. 6.1%; P = 0.02), which remained significant after adjustment for potential confounders (adjusted OR 5.2; 95% CI 1.2-23.0; P = 0.03)¹⁵³. Interestingly in this study, patients with moderate to severe OSA who were compliant with CPAP were significantly less likely to develop pre-proliferative/proliferative DR compared to non-compliant patients¹⁵³. This finding was supported by another proof of concept study that showed that CPAP treatment ≥ 2.5 h/night CPAP over 6 months in individuals with OSA and significant macular oedema was associated with improvement in visual acuity but without improvement in the oedema¹⁵⁴. Currently, RCTs assessing the impact of CPAP on DR are ongoing.

In a systematic review of 2 longitudinal and 10 cross-sectional studies there was an association between OSA and CKD in patients with T2D (pooled OR 1.73, 95% CI: 1.13-2.64)¹⁵⁵. In a longitudinal study in patients with T2D, CKD prevalence was higher in patients with OSA vs. without OSA (49.3% vs. 23.8%, P < 0.001), which remained significant after adjustment for confounders (adjusted OR 2.64, 95% CI 1.13-6.16), P = 0.02). OSA was also associated with lower eGFR and more micro- and macro-albuminuria¹⁵⁶. After an average follow-up of 2.5 (0.7) years, eGFR decline was greater in patients with vs. without OSA (median -6.8% [IQR -16.1 to 2.2] vs. -1.6% [-7.7 to 5.3%], P = 0.002)¹⁵⁶. After

311 adjustment, having OSA (B = -3.8, P = 0.044) and higher AHI (B = -4.6, P = 0.02) were predictors of
312 lower study-end eGFR¹⁵⁶.

313 The relationship between OSA and peripheral neuropathy in patients with T2D was examined in a
314 cross-sectional study, which showed that OSA is associated with peripheral neuropathy based on the
315 Michigan Neuropathy Screening Instrument (MNSI) vs. patients without OSA (60% vs. 27%, P < 0.001),
316 which remained significant after adjustment (OR 2.82; 95% CI 1.44-5.52; P = 0.003)¹⁴³. In addition,
317 OSA was associated with lower intra-epidermal nerve fibre density (based on skin biopsies), and a
318 history of foot ulceration in patients with T2D¹⁴¹. These studies suggest that OSA was associated with
319 both large and small fibre neuropathy in patients with T2D. Cohort studies and RCTs assessing the
320 relationship between OSA and CPAP on diabetes-related neuropathy and its complications are
321 ongoing.

322 OSA and T1D:

323 As patients with T1D tend to be lean or leaner than patients with T2D, examining OSA in T1D received
324 much less attention than in T2D¹⁵⁷. However, there is increasing interest in OSA in patients with T1D,
325 particularly that some recent studies suggest that OSA in T1D might be more related to autonomic
326 neuropathy rather than obesity¹⁵⁸. In addition, epidemiological studies suggest that obesity
327 prevalence is increasing in patients with T1D which might further increase their risk of developing
328 OSA¹⁵⁹.

329 In a systematic review of 4 studies (n= 186 patients), the prevalence of OSA (defined as AHI ≥ 5) was
330 51.9% among adult patients with T1D, but the 95% CI was wide (31.2-72.6) reflecting the small
331 sample size the variation between studies¹⁶⁰. The prevalence of moderate to severe OSA (AHI ≥ 15) in
332 the same meta-analysis was 16.7% (95% CI: 1.1, 34.5)¹⁶⁰.

333 Autonomic neuropathy was suggested as one potential mechanism for the high prevalence of OSA in
334 T1D as shown in a cross-sectional study of 199 patients with T1D in which OSA was present in 32% of
335 the patients with normal BMI¹⁶¹. And another study showed a higher prevalence of OSA in patients
336 with T1D and cardiac autonomic neuropathy compared to patients with T1D but without neuropathy
337 (67% vs. 23%)¹⁶². Other factors might contribute to the high prevalence of OSA in children and
338 adolescents with T1D including lower mean lung volumes (FVC, PEF, MMEF)^{163, 164} and impaired gas
339 exchange with lower diffusing capacity for carbon monoxide¹⁶⁵. There are similar findings of impaired
340 pulmonary function in adult patients with T1D¹⁶⁶⁻¹⁶⁸. The natural history, impact, and pathogenesis of
341 OSA in patients with T1D remain poorly explored and large well-designed studies are needed.

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OSA & the Renin-Angiotensin-Aldosterone System (RAAS)

The links between OSA and RAAS activation are potentially bi-directional (**Figure 5**). Hyperaldosteronism might also play an important role in the well-established links between OSA and hypertension (particularly resistant hypertension-RH) (**Figure 5**)^{9, 169-173}.

The pathophysiology of hyperaldosteronism in patients with OSA is mainly attributed to the activation of the RAAS due to cyclical/intermittent hypoxia¹⁷². In addition, some studies suggested a higher prevalence of primary aldosteronism (PA) in patients with OSA compared to patients without OSA¹⁷³.

A recent meta-analysis has examined the relationship between OSA and RAAS activation¹⁷⁴. The meta-analysis included 14 studies, all but one, were case-control studies and they included a relatively small sample size (mostly < 100, range 12 to 120)¹⁷⁴. The studies generally included middle age men and 8 of them included patients with hypertension¹⁷⁴. The meta-analysis found no significant relationship between OSA and plasma renin activity (PRA) (mean difference 0.17 ng/mL per hour (95% CI: -0.22 to 0.55, $P = 0.40$)) or plasma renin concentration (PRC) (mean difference 0.95 ng/mL (95% CI: -0.58 to 2.48, $P = 0.23$)¹⁷⁴. However, angiotensin II levels were significantly higher in patients with OSA compared to those without OSA (mean difference of 3.39 ng/L; 95% CI 2.00 to 4.79, $P < 0.00001$)¹⁷⁴. There was a trend towards higher plasma aldosterone concentration (PAC) in patients with OSA vs. no OSA (mean difference 0.95 ng/dL; 95% CI: -0.16 to 2.07, $P = 0.09$)¹⁷⁴. However, when examined in patients with and without hypertension separately, patients with hypertension and OSA had significantly higher PAC vs. patients with hypertension but without OSA (mean difference 1.32 ng/dL; 95% CI: 0.58 to 2.07, $P = 0.0005$)¹⁷⁴.

The above-mentioned meta-analyses had high heterogeneity, which could be due to variations in the definition of OSA¹⁷⁴. The heterogeneity can also be attributed to the medication used prior to RAAS measurements; however, a meta-regression showed that anti-hypertensives did not affect the relationship between OSA and PAC¹⁷⁴. Supporting the findings of this meta-analysis, another study showing that the AHI correlated significantly with PAC and urinary aldosterone levels ($r = 0.568$, $p = 0.0009$; $r = 0.533$, $p = 0.002$, respectively) in patients with RH and hyperaldosteronism¹⁷⁵.

Several uncontrolled studies in patients with hypertension (mostly RH) showed that CPAP lowered angiotensin II and aldosterone levels¹⁷⁶⁻¹⁷⁹. One RCT in which 117 patients with RH were randomised to CPAP ($n=57$) vs. no CPAP ($n=60$) showed that 6 months of CPAP resulted in greater reduction in aldosterone excretion (based on 24 h urine) compared to the control group in the per-protocol analysis (mean difference: -3.3 $\mu\text{g}/24\text{ h}$; 95% CI -6.1 to -0.4 $\mu\text{g}/24\text{ h}$; $P = 0.027$)¹⁸⁰.

374 However, the intention to treat analysis showed only a trend ($p=0.07$). The impact of CPAP on
375 lowering aldosterone was particularly evident in those with uncontrolled hypertension, non-
376 dipping in nocturnal BP, not using spironolactone, and with patients with worse hypoxia¹⁸⁰. A
377 recent meta-analysis of 3 observational studies and 2 RCTs (did not include the above-mentioned
378 RCT) showed that CPAP lowered aldosterone levels compared to no/sham CPAP (mean difference -
379 0.236, 95 % CI -0.45 to -0.02, $p = 0.034$)¹⁸¹.

380 Chronic IH seems to play an important role in the impact of OSA on the RAAS and the mechanistic
381 pathway is shown in **Figure 5**^{172,182-185,176-178}.

382 On the other hand, RAAS activation and hyperaldosteronism might lead to or worsen OSA via
383 multiple mechanisms as detailed in **Figure 5**. In a retrospective cohort registry based study, the
384 risk of developing OSA was higher in patients with hypertension and hyperaldosteronism
385 compared to those without hyperaldosteronism after adjustment for age, sex, BMI, diabetes
386 mellitus, and heart failure (adjusted OR: 1.8; 95% CI 1.3-2.6)¹⁸⁶. Moreover, in a cross-sectional
387 study of patients with RH, spironolactone treatment was associated with lower AHI¹⁸⁷. In another
388 uncontrolled study in patients with RH, spironolactone (25-50mg daily for 8 weeks) improved OSA
389 severity (based on PSG) (AHI: 39.8±19.5 vs 22.0±6.8 events/h; $P<0.05$;) ¹⁸⁸. A recent systematic
390 review and meta-analysis found 3 studies (1 RCT) and concluded that spironolactone reduced the
391 AHI by a mean of -21.12 (95% CI -27.47 to -14.77, $P<0.00001$)¹⁷⁵. Furthermore, in a small study of
392 20 patients with PA who had PSGs, having MR antagonists ($n=13$) or adrenalectomy ($n=7$) resulted
393 in AHI reduction from 22.5 (14.7) to 12.3 (12.1) ($P=0.02$)¹⁸⁵. These studies support the notion that
394 hyperaldosteronism could worsen OSA and suggest that aldosterone antagonists can be useful in
395 patients with hypertension or PA and OSA.

396 Finally, due to the links between OSA and PA the recent guidelines of the Endocrine Society on the
397 management of PA recommend that patients with hypertension and OSA are screened for PA¹⁷³.

398 Furthermore, well designed RCTs assessing the impact of MR antagonists on OSA are needed,
399 particularly that OSA is associated with increased CVD risk and that CPAP compliance is often not
400 optimal.

401 Although not directly related to RAS activation, it is important to note that patients with OSA can
402 present with hypertension and the clinical and biochemical features of pheochromocytoma without
403 the presence of a catecholamine secreting tumour (i.e. pseudo-pheochromocytoma)^{110, 189-191}. These
404 cases are rare but have been reported in multiple case reports and series, and the clinical and
405 biochemical features usually resolve with CPAP treatment or weight loss^{110, 189-191}.

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OSA & hypothalamic-pituitary-adrenal (HPA) axis

Cortisol secretion has a well described circadian rhythm and is closely related to sleep stages^{192, 193}. Sleep onset and SWS are associated with a decline in cortisol levels followed by increased cortisol secretion in late sleep (which is consistent with the rise in early morning)¹⁹⁴. On the other hand, cortisol might impact on sleep architecture, for example, HPA axis hyperactivity inhibits SWS and promotes nocturnal awakening¹⁹³.

OSA and HPA axis activation:

The impact of OSA on HPA axis is controversial with conflicting results due to the confounding effects of obesity, the sampling frequency (single time point vs. 24-hours profile), variability in matching between patients with and without OSA, small sample sizes, and short CPAP duration with variability in compliance. Some studies showed no relationship between OSA and the HPA axis, while some even suggested that OSA might inhibit the HPA axis [AHI and ODI correlated negatively with morning cortisol levels: $r = -0.444$, $P = 0.002$ and $r = -0.381$, $P = 0.011$ respectively]¹⁹⁵⁻¹⁹⁸. In a systematic review of studies that compared cortisol levels in patients with OSA to either obese or lean control, there was no evidence of HPA activation in patients with OSA in 6/7 studies¹⁹⁹. However, only 2 of these studies had plasma cortisol measurements over 24-h, while the rest had single time point measurements¹⁹⁹. The two studies that measured 24-h cortisol profile reported contradicting results as one showed no difference in mean 24-h plasma cortisol between patients with OSA and obese controls²⁰⁰, while the other showed that OSA was associated with HPA activation compared to obese controls²⁰¹.

However, the impact of OSA on HPA axis may not necessarily be consistent over the 24-h period, as the study by Vgontzas et al. showed that mean plasma cortisol levels between 23:00h and 7:00h were higher in patients with OSA and obesity vs. obese controls, consistent with nocturnal HPA activation when there is intermittent hypoxia and disruption of the sleep architecture²⁰¹ (**Figure 6**). Another important aspect is that the impact of OSA on HPA axis may not be simply related to basal or 24-h cortisol profiles but might be related to the dynamic responses to HPA inhibition or stimulation. Carneiro et al. showed that although basal salivary cortisol wasn't different between patients with OSA vs. obese controls, the salivary cortisol inhibition following overnight dexamethasone suppression test (ONDST) was significantly less pronounced in patients with OSA compared to obese controls¹⁹⁶. Interestingly, this deficit was corrected after 3 months of CPAP¹⁹⁶. Another study also showed that ACTH responses to CRH stimulation were higher in patients with OSA compared to obese and lean controls²⁰².

439 In the same above-mentioned systematic review, 8 uncontrolled studies assessed the impact of CPAP
440 on cortisol levels (blood or salivary)¹⁹⁹. Five studies showed no impact^{76, 196, 203-205}, while 3 studies
441 showed that CPAP lowered cortisol levels (blood and salivary)^{201, 206, 207}. The studies that showed
442 favourable impacts of CPA measured cortisol more frequently during the 24 hours compared to the
443 negative studies¹⁹⁹. However, a recent in-laboratory study showed that 8 hours of CPAP per night did
444 not have any effect on 24-h cortisol profile²⁰⁸. Nonetheless, this study was over a 1-week period,
445 unlike the studies that showed positive impact of CPAP on cortisol which were over 3 months period.
446 A slightly longer study of 14 days, showed that CPAP can lower morning salivary cortisol in men and
447 women with obesity and OSA²⁰⁹. The confounding effects of obesity and gender on the relationship
448 between OSA and HPA axis were addressed in a recent study of non-obese men and postmenopausal
449 women which showed that OSA patients had higher 24h blood cortisol levels compared to controls,
450 which were lowered after 2 months of CPAP⁵¹.
451 Overall, while the studies showed conflicting results there is evidence that OSA is associated with HPA
452 activation particularly nocturnally and that CPAP (14 days to 3 months) can lower cortisol 24-h profile
453 rather than cortisol levels at single time points. The effects of OSA on the HPA axis can be mediated
454 via mechanisms related to night awakenings (even when brief), sleep restriction, and intermittent
455 hypoxia^{51, 210-216} as shown in **Figure 6**.

456 OSA in patients with Cushing's syndrome:

457 Several studies have shown that OSA is common in patients with Cushing's syndrome (CS) (whether
458 endogenous or exogenous)²¹⁷. The prevalence of OSA (based on PSG) was higher in women with
459 active CS (n=35) compared to age- gender- and BMI- matched controls (n=30) (50% vs
460 23%, $P = 0.003$)²¹⁸. After controlling for BMI and HOMA score, serum cortisol remained independently
461 associated with AHI (R^2 : 77.8%, $P < 0.001$), suggesting that the relationship between CS and OSA are
462 not only related to obesity²¹⁸. A recent Taiwanese population-based cohort study showed that
463 patients with CS (n=53) were at increased risk of developing OSA compared to matched controlled
464 (matched for age, sex and comorbidities including obesity, T2D, and hypertension) (4.11 vs. 1.70 per
465 thousand person/ year; HR 2.82, 95% CI: 1.67-4.77), with slightly higher risk in men vs. women²¹⁹.
466 Interestingly in this study, the survival curves for OSA development starting separating clearly from
467 the first year after the diagnosis of CS²¹⁹. Similarly, in patients without OSA (n=17) who had PSG
468 before and after 3 months of prednisolone (10mg daily or more), AHI worsened by 56% compared to
469 controls (with mild OSA but no steroid treatment)²²⁰. This increase in AHI did not correlate with
470 changes in weight and neck circumference suggesting mechanisms other than adiposity responsible
471 for the worsening in AHI²²⁰.

472

473 While obesity might play an important role in the relationship between CS and OSA, it is clear from
474 the above-mentioned studies that obesity is not the only factor. In addition to obesity,
475 hyperglycaemia, IR, and ectopic fat (in the peritoneum, mediastinum and parapharyngeal spaces)
476 may also play a role in the increased risk of OSA in patients with CS^{217, 221}. Moreover, hypercortisolism
477 can induce UA myopathy leading to compromised UAs (**Figure 6**)^{217, 219, 222}.

478 Future studies need to assess the impact of CS treatment on the incidence and severity of OSA and to
479 examine whether the increased OSA risk in patients with CS is lifelong or simply related to the period
480 where CS is active. In addition, endocrinologists, surgeons and anesthetists need to be aware of the
481 high risk of OSA in patients with CS when considering surgical treatment (both pituitary and adrenal)
482 in order to ensure the safety of the surgical intervention.

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483 OSA & Growth Hormone (GH)/IGF axis

484 Summary of OSA impact on GH/IGF axis as well as the relation of GH excess and deficiency to OSA
485 development or worsening can be found in **Figure 7**.

487 OSA and the dysregulation of GH/IGF axis

488 OSA-associated chronic IH and disruption of sleep architecture can lead to dysregulation of the
489 GH/IGF axis as GH secretion is increased after sleep onset and during SWS (both of which are
490 disrupted in patients with OSA)^{223, 224}. Overall, studies in rodents and humans suggest that OSA is
491 associated with suppression of basal and stimulated GH and IGF-1 levels which are improved by
492 CPAP²²⁵.

493 In rodents, IH was shown to cause a recoverable dose-dependent suppression of GH release and GH
494 mRNA expression, possibly due to modulation of somatostatin activity²²⁶. In humans, OSA was shown
495 to be associated with a marked reduction in GH blood levels, which increased following one night of
496 CPAP⁶⁴. In addition, fasting IGF-1 levels correlated negatively with the ODI in men with OSA, but
497 increased following 3 months of CPAP¹⁹⁵. Sleep disruption also plays a role in the relationship
498 between OSA and the GH/IGF-1 axis. In an experimental study of patients with OSA who were
499 examined for 1 night without CPAP and 1 night with CPAP, GH plasma levels and secretion rate
500 (bloods were collected every 10 minutes over night) were reduced and increased after CPAP
501 treatment; this improvement correlated with the improvement in SWS²²⁷.

502 In support of the impact of OSA on the GH/IGF axis, a recent RCT in 65 middle-aged men with
503 moderate to severe OSA showed that CPAP vs sham CPAP increased IGF-1 levels, total and pulsatile
504 GH secretion, mean GH concentration, mass of GH secreted per pulse and pulse frequency after 12
505 weeks of treatment with further increases in IGF-1 levels and a decrease in IGFBP-1 levels by week

24²²⁸. Furthermore, other treatments that can improve OSA, such as adenotonsilectomy in children, have also been shown to improve IGF-1 and IGFBP-3 levels²²⁹.

Obesity is a potential confounder for the relationship between OSA and GH/IGF-1 dysregulation as obesity (particularly visceral) is linked to a reduction in GH secretion, IGF-1 levels and peripheral GH sensitivity, which can recover with weight loss²³⁰. However, IGF-1 levels were lower in patients with OSA compared to the weight matched control despite that both these groups had lower IGF-1 levels compared to the lean control⁹⁶.

OSA and acromegaly

Many cross-sectional studies showed that OSA is highly prevalent in patients with active acromegaly (45-80%)²³¹, with an average prevalence of 69% in PSG-based studies²³². Although lowering GH/IGF-1 improves OSA, up to 40% (range 21-58%²³¹) of those with controlled acromegaly have persistent OSA that required evaluation and the consideration of CPAP^{233, 234}. "Although clinicians seem to be aware of the links between acromegaly and OSA (as shown by a survey in Italy), only few patients undergo PSG in clinical practice²³⁵.

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In addition, OSA contributed to the adverse outcomes of acromegaly, despite that there were no differences in GH or IGF-1 levels between patients with OSA + acromegaly vs. acromegaly alone²³⁶. The presence of impaired glucose tolerance or T2D was higher in patients with acromegaly and OSA vs. acromegaly only (n: 10/17 vs. 5/19)²³⁶; although this was not adjusted for obesity. In addition, OSA contributed to insulin resistance in patients with acromegaly, which improved by CPAP in a RCT²³⁷. Furthermore, OSA might play an important role in other acromegaly-related comorbidities such as hypertension and heart failure/cardiomyopathy²³⁸.

As a result of the high prevalence of OSA and its impact on acromegaly-related comorbidities, the 2014 Endocrine Society Clinical Practice Guideline for acromegaly recommended evaluating all patients for OSA²³⁴. In addition, the guidelines recommended that patients with severe pharyngeal thickness and OSA should be treated with somatostatin receptor ligands preoperatively to reduce the OSA-related surgical risks²³⁴.

On the other hand, a recent study of 507 patients with OSA showed that 10 patients (1.97%) had elevated IGF-1 levels, of which 9 patients suppressed GH levels on OGTT giving an acromegaly prevalence of 0.2% (1/507)²³⁹. These findings suggest that screening for acromegaly in OSA should not be routinely performed. However, if in addition to OSA, there are other features of acromegaly or acromegaly-associated conditions (such as T2D, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis, and hypertension), then measurement of IGF-1 levels is recommended as per the Endocrine Society Clinical Practice Guideline for acromegaly²³⁹. Finally, although we have focused

here on OSA, central sleep apnoea (SA) can also occur in the context of acromegaly²⁴⁰, but far less common than OSA²³⁶.

542

The mechanisms leading to the high prevalence of OSA in patients with acromegaly are summarised in **Figure 7**^{231, 234, 240-254}.

545 **The impact of Acromegaly treatment on OSA:**

546 Considering that OSA is driven by the excess of GH/IGF-1 in patients with acromegaly, it is not
547 surprising that treating acromegaly can improve OSA but it is also common for OSA to persist or even
548 worsen after acromegaly is brought under control²³⁴. In a small study of 6 patients with SA syndrome
549 (obstructive or central with EDS) and acromegaly, trans-sphenoidal adenomectomy resulted in
550 resolution of the SA syndrome in all patients regardless of whether acromegaly was cured or not²⁵⁵. In
551 another study of 24 patients with acromegaly (20 with OSA) who had remission following trans-
552 sphenoidal surgery; at 1 month post-surgery, the tongue area declined while the airway volume
553 increased significantly, accompanied with improved OSA²⁵⁶. The prevalence of severe OSA was
554 reduced from 45.8% to 28% by 6 months with significant improvements in AHI but the average AHI
555 remained in the moderate OSA range²⁵⁶. Similar results were observed in patients with acromegaly
556 following treatment with somatostatin analogues^{246, 249, 257-260} and pegvisomant^{261, 262}.

557 The above-mentioned studies clearly show that curing acromegaly or significant improvements in
558 GH/IGF-1 levels can improve OSA, but many patients with acromegaly have persistent moderate to
559 severe OSA that might require CPAP. In fact, OSA might occur in patients with acromegaly following
560 achieving normal IGF-1 levels even when OSA was not present at baseline as shown by Chemla et al
561 (OSA cured in 57%, new OSA that was not present at baseline 22%)²⁶³. Similarly, Castellani et al.
562 showed that AHI increased in 55.5% of patients with acromegaly after complete/ partial biochemical
563 control (either after surgery, radiotherapy, and/or medical therapy)²³¹. OSA persistence following
564 acromegaly treatment is probably due to multiple factors including increased BMI and/ or irreversible
565 craniofacial-skeletal deformities/fibrosis²³¹. Hence, OSA evaluation is needed post acromegaly
566 treatment regardless of the normalisation of GH/IGF-1²⁶⁴.

567

568 **OSA in adults with GH deficiency (GHD):**

569 OSA is much less examined in GHD in comparison to acromegaly. OSA is very common in adults with
570 GHD with a prevalence of 63%; which is mainly due to the increased obesity either due to GHD or
571 hypothalamic obesity as a result of surgical or radiotherapy treatment delivered to the underlying
572 pituitary or hypothalamic pathology²⁶⁵.

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573 **GH replacement and OSA:**

574 GH replacement in patients with GHD might improve OSA due to a reduction in adiposity (strong
575 lipolytic properties of GH^{266, 267}) or it could worsen OSA if the replacement was excessive. The studies
576 in the literature show a mixed picture. In a small study of 5 men who received GH replacement
577 (median dose 2 U/day; median serum IGF-I 351 mcg/l) for 1-2 years post pituitary surgery GHD,
578 showed that 6 months after stopping GH treatment the median obstructive AHI decreased
579 significantly from 4.4 to 0.1 (P = 0.03) whereas the central AHI increased from 6.3 to 14.6 (P = 0.03);
580 suggesting that GH replacement worsened the OSA but improved central SA²⁶⁸. However, another
581 study of 19 patients with GHD showed that GH replacement for 6 months had no impact on AHI (pre
582 vs post treatment: 28.2/h vs. 28/h), regardless of baseline OSA status²⁶⁵. Still, in a large observational
583 longitudinal study of GH-treated (n = 1988) and untreated (n = 442) patients with GHD showed that
584 after a mean follow up of 2.3 years the sleep apnoea incidence was greater in the group that received
585 GH replacement (3.3% vs 0.9%, p<0.05), despite that the GH treated vs. untreated groups had similar
586 BMI at baseline and the GH-treated group were younger²⁶⁹. However, the GH-treated group had
587 higher baseline IGF-1 levels (108 ± 61 vs. 90 ± 51 mcg/l, p <0.001) and serum IGFBP-3 levels (2.4 ± 0.9
588 vs. 2.1 ± 1.0 mcg/l, p<.001)²⁶⁹. In a 12-month double blind RCT of 40 men with obesity and
589 dysglycaemia who were randomised to either GH or placebo; GH treatment increased IGF-1 from
590 168±72 to 292±117 mcg/L, the AHI from 31±20 to 43±25 and the ODI from 18±14 to 29±21 (all p
591 values ≤ 0.001)²⁷⁰. Interestingly, GH treatment in this study increased neck transverse diameter,
592 circumference, and total cross-sectional area, while reduced abdominal visceral adipose tissue (based
593 on CT)²⁷⁰.

594
595 Hence, more data is required to assess the impact of GH replacement on pre-existing OSA and the
596 development of new OSA. However, GH replacement might result in the development or worsening
597 of pre-existing OSA via increasing IGF-1 levels or via affecting adipose tissue distribution (increasing
598 neck circumference).

600 **OSA in Prader -Willi syndrome**

601 ▲ Children and patients with Prader-Willi syndrome (PWS) are also at high risk of having OSA
602 (prevalence: 1:10,000- 25,000 live children), and as a result screening for OSA in this population has
603 been recommended²⁷¹. ▲ The high prevalence of OSA in patients with PWS is likely to be multifactorial
604 due to GH deficiency, increased viscosity of upper airways secretions, craniofacial abnormalities with
605 small airways, upper airways muscles hypotonia and secondary alveolar hypoventilation (obesity and
606 scoliosis causing lung volume restriction) all leading to airway collapsibility²⁷¹ ▲

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607 The impact of GH replacement on OSA in children with PWS is debatable. Salvatoni et al. showed that
608 short-term treatment with rhGH (6 weeks) did not worsen the AHI and there was no difference in
609 AHI between the treatment and control group at baseline or study-end²⁷². Nonetheless, in this
610 study, the AHI increased (i.e. OSA worsened) in 50% of the cases following GH replacement²⁷².
611 Similar results were shown in another study suggesting that the AHI worsen in a subgroup of
612 patients following GH replacement over the short run²⁷³; which in part could be due to the
613 development of adenotonsillar hypertrophy following GH treatment²⁷³. However, longer term follow-
614 up (2 years) showed that GH replacement did not worsen AHI during the follow up except in those
615 who worsened shortly after GH initiation^{274, 275}. As a result, the 2013 consensus guidelines considered
616 untreated severe obstructive sleep apnea as an exclusion criteria for rhGH initiation, till the patient is
617 treated with CPAP^{276, 277}. This is particularly important considering that sudden death early in the
618 course of GH replacement in patients with PWS, associated with sleep disordered breathing/OSA,
619 have been reported in the literature²⁷⁸⁻²⁸⁰.

621 OSA & hypothalamic-pituitary-thyroid (HPT) axis

622 OSA in patients with hypothyroidism

623 A recent systematic review of 1 observational and 5 interventional studies (501 patients in their 4th-
624 5th decade of life) found that 25-50% of patients with overt hypothyroidism (OH) had nocturnal
625 breathing abnormalities (snoring, choking, apnoea periods); which improved with levothyroxine 4
626 (LT4) treatment²⁸¹. In one study, 30% of patients with recently diagnosed OH had evidence of OSA
627 (AHI ≥ 5 based on PSG), and LT4 improved the AHI (from a median of 14.3 (7.4–33.6) to 2.1 (0.8–
628 4.6))²⁸². In addition, in the later study LT4 treatment improved hypoxaemia and sleep architecture
629 (TpO2 sat<90%: 14% (2.2–19.9) vs 0.2% (0–1.7), p<0.05; SWS%: 18.4 (7.2–25.2) vs 28.2 (15–33.4),
630 p<0.05)²⁸². This suggests that hypothyroidism can lead to/worsen OSA which improves with LT4
631 treatment. However, larger studies including RCTs are needed before confirming this relationship.

632 There is lack of good quality data regarding the relationship between OSA and subclinical
633 hypothyroidism (SH); one small observational study (n=108) showed that 53% of patients with
634 untreated SH had OSA (based on PSG)²⁸³. However, these results are likely to represent selection bias
635 as the prevalence of OSA in healthy controls with normal thyroid functions was higher (75%) than
636 that in patients with untreated SH despite that SH patients were heavier and the patients recruited
637 from the respiratory department²⁸³. Hence, currently we cannot be certain about the relationship
638 between OSA and SH.

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639 Hypothyroidism in patients with OSA

640 While studies are not consistent, overall there is no evidence that hypothyroidism is more common in
641 patients with OSA compared to patients without OSA^{284, 285}. A recent study also supported this
642 conclusion as it showed that the prevalence of raised TSH in 813 patients with severe OSA was 4.7%
643 which is similar to the general population²⁸⁶. Some studies showed that the prevalence of SH was
644 higher in OSA vs. control, but these studies have potential selection bias as the population was
645 recruited from sleep clinics and the control group was younger and leaner²⁸⁷⁻²⁸⁹. Other studies did
646 not show a high prevalence of SH in patients with OSA²⁹⁰. In a study of 245 euthyroid patients with
647 suspected OSA, the prevalence of Hashimoto's thyroiditis was 32.2% in patients without OSA vs.
648 46.8% in patients with OSA (based on PSG) ($p=0.03$)²⁹¹. The prevalence of Hashimoto's increased with
649 worsening severity of OSA²⁹¹.

650 Mechanisms linking OSA and thyroid disorders:

651 Hypothyroidism can lead to the development or worsening of OSA via multiple mechanisms
652 summarized in **Figure 8**^{232, 281, 282, 284, 291-300}.

653 OSA and non-thyroidal illness syndrome (NTIS)

654 A recent cross-sectional study showed that patients with moderate to severe OSA (n=125) had a
655 higher prevalence of NTIS (defined as normal TSH and low FT3) compared to controls (n=60) (10.4%
656 vs. 0%), but the control group was lean and there were more men in the OSA group³⁰¹. Within the
657 OSA group, patients with NTIS had worse nocturnal hypoxemia compared to patients without NTIS³⁰¹.
658 This suggests that IH could play a role in the high prevalence of NTIS in patients with OSA, possibly
659 via down-regulation of deiodinase 1 and enhancing deiodinase 3 inactivating T3 and T4³⁰². In
660 addition, oxidative stress and low grade inflammation, resulting from OSA, can also contribute to the
661 association between OSA and NTIS^{303, 304}. CPAP for 5 months has been shown to improve FT3 levels in
662 patients with NTIS supporting the notion that OSA might lead to NTIS, but this study was not
663 controlled³⁰¹. However, it is important the clinicians take into account the possibility of NTIS when
664 interpreting thyroid function results in patients with OSA.

665 In summary, sleep apnoea and thyroid specialists need to have a low threshold to test for thyroid
666 disorders if indicated clinically. In addition, OSA can be associated with NTIS and clinicians
667 interpreting the thyroid function results need to take the presence of OSA into consideration.
668 However, cohort studies with well-matched control groups and RCTs are needed to enable us to
669 understand the complex relationship between OSA and HPT axis and the impact of treating one or the
670 other.

OSA & the Hypothalamic-Pituitary-Gonadal (HPG) axis

The interaction between sex hormones and OSA was initially brought to attention by the consistently reported a higher prevalence of OSA in men vs. women. This relationship was further emphasized by several observations including that testosterone replacement in men worsens/ increases the risk of having OSA, the prevalence of OSA in postmenopausal women was higher than in premenopausal women; hormone-replacement therapy reduced the risk of OSA in postmenopausal women and oral contraceptives were associated with lowered OSA risk in women with polycystic ovarian syndrome (PCOS)^{65, 305}.

In Men

OSA is associated with hypogonadotropic hypogonadism due to altered gonadotropin synthesis and release³⁰⁶. In a cross-sectional analysis of a prospective study of healthy older men (n=1312, ≥65years old), lower testosterone levels (based on quartiles) were associated with significantly less SWS, higher AHI (based on PSG) and more sleep time spent with O2 sat<90% after adjustment for age and race³⁰⁷. However, adjustment for BMI made these associations non-significant³⁰⁷. Other studies showed that patients with OSA had lower area under the curve and mean levels for LH (24.9 ± 10.2 IU/l h vs. 43.4 ± 9.5 IU/l, $P < 0.005$) and testosterone (67.2 ± 11.5 nmol/l vs. 113.3 ± 26.8 nmol/l, $p=0.003$) compared to healthy controls, but the control group was leaner numerically³⁰⁸. Similar findings were found in other studies³⁰⁹⁻³¹¹.

Testosterone replacement and OSA

Patients receiving testosterone replacement are at increased risk of developing OSA. In a cohort study, 3422 of US military service members, aged 40-64 years, who were free of OSA at baseline and received testosterone replacement, were matched based on age and comorbidities to men who did not receive testosterone treatment³¹². The absolute 2-year risk of incident OSA was greater in patients that received testosterone replacement vs those who did not (16.5% (95% CI: 15.1–18.1) vs 12.7% (95% CI: 11.4–14.2), $p<0.001$)³¹². Interestingly, the increased risk of OSA was greater for those who used injectable vs topical testosterone³¹². This is also supported by a small RCT in which healthy ambulatory men aged > 60 years were randomised to receive three injections of weekly intramuscular testosterone esters (500 mg, 250 mg, and 250 mg) or matching oil-based placebo and then crossed over to the other treatment after 8-week washout. Testosterone replacement in this RCT resulted in worsening RDI (approximately by 7 events per hour), mainly during non-rapid eye movement (NREM) sleep, and worsened nocturnal hypoxaemia measures; while placebo had minimal effects on RDI and hypoxia parameters³¹³. Several other studies suggested a link between testosterone replacement and incident or worsening OSA³¹⁴⁻³¹⁷. As a result, the Endocrine Society

clinical practice guidelines recommended against the use of testosterone replacement in men with untreated severe OSA³¹⁸. It is unclear whether different methods of testosterone replacement have a differential impact on the risk of developing or worsening OSA due to the variations in the pharmacokinetics profiles of these agents.

The effects of testosterone can be time-limited as shown in a RCT of 67 men who received hypocaloric diet and were randomised to intramuscular injections of 1000 mg testosterone undecanoate or placebo³¹⁹, in which testosterone replacement worsened the ODI by 10.3 events/h (95%CI, 0.8–19.8 events/h; P = 0.03) and on nocturnal hypoxaemia at 7 weeks but not at 18 weeks³¹⁹. This time dependent effects might be as a result of time dependent changes in hyperoxic ventilatory recruitment threshold following testosterone replacement³²⁰.

Mechanisms

Low testosterone in men can lead to loss of muscle mass and increased visceral adiposity, which can contribute to the increased/worsening OSA in men with hypogonadism^{321, 322}. It is unclear how testosterone replacement leads to OSA, but postulated mechanisms include altered ventilator responses such as increased response to hypoxaemia (leading to CO₂ levels below apnea threshold), reduced sensitivity to hypercapnia, or anabolic effects (leading to UA narrowing) and an effect on the neuromuscular control of UA^{323, 324}. However, these mechanisms are not well proven with multiple studies showing conflicting results. In one interesting mechanistic study, androgen blockade with flutamide did not influence chemo-responsiveness to hypoxia/ hypercapnia³²⁵.

In addition, OSA can impact the HPG axis via several mechanisms including IH, sleep fragmentation and obesity^{306, 310, 326}. Testosterone levels peak during REM (fewer REM sleep episodes and REM sleep latency are related to lower testosterone concentrations³²³), hence the disruption of sleep architecture in OSA (loss of REM) might explain the link between OSA and low testosterone¹⁹³.

The impact of OSA treatment on the HPG axis:

CPAP effects on the HPG axis in men remains controversial with a limited number of studies in the literature. A meta-analysis in 2014 found only 2 RCTs and 5 observational studies with a total sample size of 232 men showing the paucity of available data³²⁷. In this meta-analysis, an average of 6 months of CPAP treatment had no effects on testosterone levels despite good CPAP compliance (standardized mean difference (SMD) = -0.14, 95%CI: -0.63 to 0.34)³²⁷. CPAP also had no effects on free testosterone or SHBG levels³²⁷.

Summary of the trials assessing the impact of OSA treatment (CPAP and surgical) on HPG axis can be found in Table 1 (^{195, 205, 328-335}). The 2 RCTs showed no effect of CPAP on testosterone levels, but the study participants did not have hypogonadism at baseline and the CPAP duration was short. The

uncontrolled studies mostly showed no effects of CPAP on testosterone levels except 2 studies, that showed that CPAP increased testosterone levels (Table 1). In one of these studies, the increase in total testosterone was associated with increased SHBG which suggest that the impact of free testosterone was rather limited. In the other study, patients had hypogonadism at baseline and CPAP improved testosterone levels along with LH, but the impact on SHBG was not reported (Table 1). Hence, the impact of CPAP on HPG axis in men remains unclear but future trials need to consider the potential difference in response between men with and without hypogonadism and need to ensure adequate CPAP treatment duration and the impact on free testosterone. It is Important to note that CPAP might still have beneficial impacts on scores for sexual and erection function despite the lack of impact of hormonal measurements^{332, 333}. However, in two RCTs sildenafil was superior to CPAP in regards to ED^{336, 337}.

In women

OSA impact on the HPG axis in women is less well studied compared to men. Based on animal studies sex hormones can influence breathing not only via androgens but also via the effects of progesterone and estradiol on CB and the brainstem³³⁸. In addition, lack of progesterone receptor in rodent led to reduced hypoxic ventilator response³³⁹ and lower UA resistance was found in the luteal phase in healthy premenopausal women with the peak in progesterone secretion³⁴⁰. On the other hand, OSA has a negative effect on female sex hormones and on sexual function and is associated with PCOs.

In a cohort of 53 women (24-72 years old), AHI>10/hr was associated with lower morning levels of 17-OH-progesterone, progesterone and estradiol³⁴¹. However, hormone replacement therapy (HRT) in post-menopausal women was associated with lower prevalence of moderate to severe OSA prevalence compared to women not taking HRT and less time spent in oxygen saturations < 90%, particularly in women who received combined estrogen-progesterone vs. estrogen alone³⁴². The impact of CPAP on the HPG axis in women remains to be explored in large studies, and since one small uncontrolled study showed no effect³³⁰ RCTs in this area are needed.

Similar to men, OSA has been associated with sexual dysfunction (FSFI score: desire, arousal, lubrication, orgasm, satisfaction, and pain) in pre- and post- menopausal women compared to matched controls^{343, 344 345}. Unlike in men, evidence for CPAP impact on sexual dysfunction in women is lacking³⁴⁶. In this review we did not discuss the impact of OSA on pregnancy.

OSA & Polycystic Ovarian Syndrome (PCOS)

OSA is highly prevalent in women of reproductive age with PCOS. A recent systematic review and meta-analysis from our group (15 studies, n=568) showed that 36.1% (95% CI: 22.4-51.0) of women

with PCOS had OSA regardless of the PCOS definition used³⁴⁷. In addition, OSA prevalence was significantly higher in obese women with PCOS compared to lean (OR: 3.96, 95%CI: 1.29-12.13) and in adult women compared to adolescents, both of which are expected since obesity and age are main risk factors of OSA, and thus PCOS precedes OSA development³⁴⁷. However, in this meta-analysis there was significant heterogeneity among studies, most studies came from the USA in women with obesity (class II) and there is a high level of selection bias since controls came from general population while exposed cohorts were recruited from specialised clinics³⁴⁷. It is plausible that in some cases the OSA could precede PCOS development as detailed in a recent study showing that 1/3 of adolescent girls with PCOS had previous tonsillar enlargement/ tonsillectomy³⁴⁸.

It is also interesting that although androgens are considered to impact OSA pathogenesis, contributing to the higher OSA prevalence in women with PCOS, three studies showed that women with PCOS and increased androgens did not have higher prevalence of OSA compared to controls, and the relationship between OSA severity and hyper-androgonaemia were not consistent across the studies³⁴⁷. This could be due to the low circulating androgen levels in women with PCOS compared to men.

In another meta-analysis from our group comparing women with PCOS and OSA vs women with PCOS only showed that the earlier group had higher BMI (mean difference: 6.01 kg/m², 95% CI: 4.69-7.33), waist circumference (MD: 10.93 cm, 95% CI: 8.03-13.83), IR (HOMA-IR: MD=2.23, 95% CI: 1.41-3.06; I²=0%), systolic BP (10.8 mmHg 95%CI 6.21 – 15.39), diastolic BP (4.63 mmHg 95%CI 1.06 – 8.21), impaired glucose tolerance (2 hour plasma glucose on OGTT: MD=2.23, 95%: 0.67-2.11, I²=0%) and worse lipids profile (higher total cholesterol, LDL, and triglycerides and lower HDL) compared to the alter group³⁴⁹. The androgen levels were not different between the two groups but hirsutism was worse in the OSA group³⁴⁹. However, these studies included were relatively small, at high risk of selection bias, and did not account for important potential confounders such as obesity³⁴⁹.

Several mechanisms link PCOS to OSA as summarised in **Figure 9**³⁵⁰.

OSA & Bone metabolism

Although cross-sectional studies assessing the relationship between OSA and bone mass density (BMD) showed conflicting results³⁵¹⁻³⁵⁴; longitudinal studies showed an increased risk of osteoporosis in patients with OSA^{355, 356}. In a large retrospective cohort study of 1377 patients with newly diagnosed OSA and 22655 matched controls (age, sex and index date), the risk of osteoporosis was greater in patients with OSA vs. control in both men and women (incidence rate: 2.52/1000 person-years vs. 1.00/1000 person-years, adjusted HR 2.74, 95% CI: 1.69-4.44) over the 6-year follow-up³⁵⁵.

803 The HR in this study was adjusted for: age, gender, diabetes status, obesity, CVD risk factors, CKD,
804 CVD, gout, and social demographics.

805 Consistent with the increased risk of osteoporosis in patients with OSA, several studies suggested that
806 OSA might increase the risk of fractures, although these studies examined conditions that are related
807 to OSA rather than OSA per se. In a study of 2911 men older than 67 years-old, men who spent $\geq 10\%$
808 of their sleep time with O_2 saturations $< 90\%$ had increased risk of incident non-spinal fractures
809 compared to men spent $< 1\%$ of sleep time with O_2 saturation $< 90\%$ over 7 years follow-up (adjusted
810 relative hazards 1.42, 95% CI 0.94- 2.15, $p=0.047$)³⁵⁷. In the same study, the relative risk of having ≥ 1
811 fall was also higher in the group with nocturnal hypoxaemia (relative risk 1.25, 95%CI 1.04 – 1.51)³⁵⁷.
812 Another longitudinal study that followed up 8101 women aged 69 years or older for 6 years found
813 that self-reported daily napping was associated with increased risk of incident hip fractures compared
814 to women who did not nap daily (age-adjusted HR: 1.29, 95%CI 1.02-1.65; fully-adjusted HR 1.33,
815 95%CI 0.99-1.78) and similar to the previous study there was an increased risk of falls in women who
816 napped daily³⁵⁸. In a recent cohort study women ($n=3220$) and men ($n=2969$) aged 40 years and
817 older, severe snoring (a common OSA symptom) was associated with increased risk of fractures over
818 10 years follow up in women (adjusted HR: 1.68, 95% CI: 1.16-2.43, $p=0.006$), with similar non-
819 significant trend in men³⁵⁹.

820 Consistent with the increased risk of osteoporosis and fractures in patients with OSA, bone resorption
821 markers (such as serum C-terminal telopeptide of type I collagen CTX) has been shown to be higher in
822 patients with OSA compared to controls in men and the AHI was independently associated with
823 urinary CTX independently of age, BMI and other variables^{352, 360}. Furthermore, CPAP for 3 months
824 lowered the creatinine adjusted urinary CTX levels significantly (211 ± 107 vs. 128 ± 59
825 $\mu\text{g}/\text{mmol}/\text{creatinine}$; $p<0.01$)³⁶⁰.

826 Several mechanisms might explain the impact of OSA on bone turnover, bone density and fractures
827 risk summarized in **Figure 10**³⁶¹⁻³⁷³.

828

829 Summary and conclusion:

830

831 In this review we have demonstrated that there are multiple bi-directional interactions between OSA
832 and the endocrine system although the observed relationships varied depending on the endocrine
833 system examined. The impact of OSA on the endocrine system was mostly mediated by intermittent
834 hypoxaemia, sympathetic activation, the elevated blood pressure and the increased inflammation

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835 and oxidative stress. While the impact of the endocrine system on OSA was mostly mediated via
836 increased upper body adiposity, narrowing of the upper airways, weakening of upper airway muscles,
837 changes to chemosensitivity and ventilatory drive as well as autonomic dysfunction.

838 Our review also shows that there are multiple knowledge gaps in the field at a mechanistic level and
839 also due to the lack of well-designed cohort and interventional studies in many areas. This is further
840 complicated by the difficulty in achieving good compliance with CPAP in clinical studies, the diurnal
841 nature of the endocrine system and the interaction between OSA and other sleep disorders such as
842 short sleep duration and misalignment in the circadian rhythm. In particular, our review found the
843 following need to be explored in future studies due to either no, minimal, or inconsistent evidence
844 currently available: the impact of OSA and CPAP on weight, the impact of Diabetes treatment on OSA
845 as well as the impact of OSA on diabetes-related outcomes, the impact of primary aldosteronism
846 treatment on OSA, the effects of OSA on the HPA axis and the natural history of OSA and its response
847 to treatment in patients with Cushing's syndrome, the long term impact of GH replacement on OSA as
848 well as central SA, the impact of thyroxine replacement on OSA in patients with hypothyroidism, the
849 relationship between OSA and subclinical hypothyroidism, the impact of long term testosterone
850 replacement and the different methods of replacement on OSA, the impact of OSA and CPAP in
851 women with PCOS and men with hypogonadism, and the impact of CPAP on bone metabolism.

852 Finally, clinicians treating patients with endocrine conditions should not assume that OSA would
853 recover by curing the underlying endocrine disorder (such as Cushing's, acromegaly or
854 hypothyroidism) and that OSA status need to be clarified by formal testing following the successful
855 treatment of the endocrine condition. Furthermore, clinicians, surgeons and anesthetists involved in
856 the treatment of the endocrine conditions that are associated with OSA need to be aware of this
857 association and treat the OSA in order to improve the safety of the general anaesthesia and surgical
858 procedures.

859

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870 **Abbreviations:**
871 American Academy of Sleep Medicine (AASM)
872 Adrenocorticotrophic hormone (ACTH)
873 Advanced Glycation End Product (AGE)
874 Apnea- Hypopnea index (AHI)
875 AngII Receptor Type 1 (AT1)
876 Body Mass Index (BMI)
877 Blood Pressure (BP)
878 Bone Mineral Density (BMD)
879 Bone Turnover Markers (BTMs)
880 Chronic Kidney Disease (CKD)
881 C-terminal telopeptide of type I collagen (CTX)
882 Continuous Positive Airway Pressure (CPAP)
883 Cushing's Syndrome (CS)
884 Diabetic Retinopathy (DR)
885 Excessive Daytime Sleepiness (EDS)
886 Electroencephalogram (EEG)
887 Epworth Sleepiness Scale (ESS)
888 Forced Vital Capacity (FVC)
889 Forced Expiratory Volume in the first second (FEV1)
890 Fasting Plasma Glucose (FPG)
891 Growth hormone (GH)
892 GH deficiency (GHD)
893 Hypoxia-Inducible Factor (HIF)
894 Hormonal Replacement Therapy (HRT)
895 Homeostatic Model Assessment for Insulin resistance (HOMA-IR)
896 Intermittent Hypoxia (IH)
897 Insulin Resistance (IR)
898 Intravenous Glucose Tolerance Test (IVGTT)
899 Laparoscopic Adjustable Gastric Banding (LAGB)
900 Levothyroxine 4 (LT4)
901 Maximum Mid Expiratory Flow Rate (MMEF)
902 Mineralocorticoid Receptors (MR)
903 Non-Alcoholic Fatty Liver Disease (NAFLD)
904 Non-rapid eye movement sleep (NREM)
905 Oral glucose Tolerance Test (OGTT)
906 Overnight Dexamethasone Suppression Test (ONDST)
907 Oxygen Desaturation Index (ODI)

908 Obstructive Sleep Apnoea (OSA)
909 Parathormone (PTH)
910 Primary Aldosteronism (PA)
911 Prader-Willi syndrome (PWS)
912 Poly ADP Ribose Polymerase (PARP)
913 Peak Expiratory Flow (PEF)
914 Percutaneous Coronary Intervention (PCI)
915 Protein Kinase C (PKC)
916 Progesterone (PRG)
917 Polysomnography (PSG)
918 Randomized Controlled trial (RCT)
919 Reactive Oxygen Species (ROS)
920 Renin-Angiotensin-Aldosterone System (RAAS)
921 Respiratory Arousal Threshold (RAT)
922 Respiratory Disturbance Index (RDI)
923 Rapid Eye Movement (REM) sleep
924 Resistant Hypertension (RH)
925 Sleep Apnoea (SA)
926 Sex-Hormone Binding Globulin (SHBG)
927 Short Sleep Duration (SSD)
928 Vital Capacity (VC)
929 Slow Wave Sleep (SWS)
930 Type 1 Diabetes (T1D)
931 Type 2 Diabetes (T2D)
932 Upper Airway (UA)
933 Upper Airways (UAs)

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1993

1994 **Figures-Legends & text:**

1995

1996 **Figure 1:** Hypnograms and sleep stages of a healthy individual (top) and a patient with OSA (bottom).
1997 Please note how the patient with OSA has disrupted sleep architecture with loss of REM and SWS.
1998 REM: Rapid Eye Movement; SWS: Slow Wave Sleep

1999

2000

2001 **Figure 2: OSA & Obesity Interplay. A.** The potential mechanisms linking obesity to obstructive sleep
2002 apnoea. **B.** The potential impact of obstructive sleep apnoea and its treatment on weight and the
2003 underlying mechanisms. Red boxes are the mechanisms of OSA that might lead to weight gain; Dark

blue boxes are the mechanisms of possible weight loss in OSA.
UA: Upper Airways; TNF-A: Tumour Necrosis Factor- Alpha; IL-6: Interleukin-6; CNS: Central Nervous System; EDS: Excessive Daytime Sleepiness; CPAP: Continuous Positive Airway Pressure

Obesity can lead to increased UA collapsibility via increased parapharyngeal fat deposition, UA narrowing, intramuscular fatty deposits leading to reduced UA muscles activity and increased UA muscle fatigability, and reduced lung volume resulting in reduced tracheal caudal traction¹⁹⁻²⁷. In addition, the low lung volume in obesity can lead to hypoxaemia and ventilatory instability in the presence of increased whole body oxygen demand due to obesity (high loop gain)²⁸. Obesity is also associated with leptin resistance, which could inhibit the respiratory drive as leptin is a respiratory stimulant^{23, 29, 31}. Furthermore, visceral adiposity can affect the neural respiratory control and the responsiveness of the chemoreceptors, through neurohormonal and inflammatory mechanisms (such as (TNF) α , and IL-6)^{26, 30, 32}, but OSA itself can further worsen inflammation and possibly oxidative stress, therefore, leading to a vicious cycle^{23, 26, 33}.

Figure 3: The potential bi-directional relationship and the underlying mechanisms between obstructive sleep apnoea and Type 2 Diabetes. SWS: Slow-wave-sleep; CB: Carotid body; FFA: Free fatty acid; ROS: Reactive oxygen species; NAFLD: Non-Alcoholic Liver Disease; HPA: Hypothalamic Pituitary Adrenal Axis; T2D: Type 2 Diabetes

IH and sleep disruption result in increased oxidative stress and inflammation leading to IR an β - cell dysfunction. In addition, OSA can impact multiple hormones that can lead to dysglycaemia including: via activation of the Hypothalamus-pituitary- adrenal (HPA) axis, changes in the Growth hormone (GH)/IGF axis, hyperaldosteronism (via hypokalaemia, increased oxidative stress and inflammation), increased ghrelin, increased leptin and reduced adiponectin^{40, 48, 90-95}. Interestingly, CPAP treatment can interrupt most of the above mentioned pathways which might explain the favourable effects of CPAP on IR⁹⁶. However, the impact of CPAP on leptin and adiponectin has not been consistent between the different studies⁹⁷⁻¹⁰¹. Furthermore, patients with OSA (due to recurrent microarousals, the loss of SWS and the IH⁵⁹) have increased sympathetic activity which can contribute to the increased IR^{30, 102}. Several factors contribute to the sympathetic overactivation in OSA including the recurrent microarousals, the loss of SWS and the IH⁵⁹. The IH, via oxidative stress and its impact on HIF signaling, results in carotid body chemosensory reflex and hence to increased sympathetic activity¹⁰³, that is reversible by CPAP^{104, 105}. Another mechanism that links OSA to dysglycaemia is the

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2037 increased risk of Non-alcoholic fatty liver disease (NAFLD) and progression to steatosis in those
2038 patients, due to ectopic fat accumulation and hepatic inflammation, with subsequent effects on
2039 insulin sensitivity^{106, 107}. A recent meta-analysis of nine cohort studies showed that OSA was a
2040 predictor of the development and progression of NAFLD (based on liver enzymes and histology)¹⁰⁷.

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2041
2042
2043 On the other hand, dysglycaemia could lead to OSA. One plausible mechanism in patients with pre-
2044 diabetes or diabetes is autonomic neuropathy, which might impact on UA innervation⁶, ventilatory
2045 drive and central respiratory responses to hypercapnia^{109, 110}. In addition, T2D is associated with
2046 reduced pulmonary volumes, forced vital capacity FVC, Forced Expiratory Volume in the first second

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2047 FEV1 and vital capacity VC) and functions compared to healthy individuals which could affect UA
2048 stability¹¹¹⁻¹²¹. A meta-analysis of cross-sectional studies showed that diabetes is associated with a
2049 modest but significant impairment of pulmonary function (in restrictive pattern)¹²² and diffusion

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2050 capacity for carbon monoxide^{112, 113, 122, 123}. The impact of T2D on the lungs seems to be related to the
2051 severity of hyperglycaemia independently of obesity and smoking¹²³; which raises the possibility that
2052 improvements in glycaemic control might have a favourable impact on OSA but this needs to be
2053 examined. Furthermore, treatment intensification in patients with T2D is often associated with
2054 weight gain¹²⁴, which could lead to the development or worsening of OSA^{10, 125}. Other independent
2055 predictors of incident witnessed apneas such as HOMA-IR, hypertriglyceridaemia, and smoking are
2056 also common in patients with T2D and thus can have a negative impact on OSA^{6, 108}.

2057
2058 **Figure 4: A. Mechanisms relating obstructive sleep apnoea to cardiovascular disease (A)**
2059 **and microvascular complications** Adapted from Jullian-Desayes et al. with permission **(B) in**
2060 **patients with Type 2 diabetes.** Adapted from Tahrani et al. with permission. CRP: C-reactive
2061 protein; IH: intermittent hypoxia; NO: nitric oxide; NOx: total nitrate and nitrite; OSA: obstructive
2062 sleep apnea; PKC: protein kinase C; AGE: advanced glycation end product; PARP: poly ADP ribose
2063 polymerase; AR: aldose reductase; GAPDH: glyceraldehyde 3-phosphate dehydrogenase.

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2064 **Fig. 4.A.** Obstructive sleep apnea and its cardiometabolic consequences.. Adapted from Kohler et al.,
2065 2010 and Lavie et al., 2009¹⁴⁰. IH, oxidative stress and inflammation play a key role in OSA and the
2066 development of associated cardiometabolic morbidities. Oxidative stress induces inflammation, while
2067 increased proinflammatory cytokines, adhesion molecules and procoagulant activities can exacerbate
2068 oxidative stress. This vicious circle leads to cardiovascular morbidity. Sympathetic overactivity and the

2069 decrease in NO induced by oxidative stress lead to hypertension. Both hypertension and
2070 inflammation promote endothelial dysfunction responsible for atherosclerosis, which in turn can also
2071 exacerbate oxidative stress¹⁴⁰. In addition, intrathoracic pressure swings and the increase in
2072 transmural pressure gradients over vessel walls could also contribute to the endothelial dysfunction
2073 observed in OSA. Recurrent arousals also activate the sympathetic nervous system and thus lead to
2074 endothelial dysfunction¹⁴⁰.

2075 **Fig. 4.B.** Both OSA and hyperglycaemia share similar molecular consequences including oxidative
2076 stress, PKC activation and AGE production. Our own work has shown that patients with OSA and type
2077 2 diabetes have increased oxidative and nitrosative stress increased PARP activation and impaired
2078 microvascular function compared with patients with type 2 diabetes only¹⁴¹.

2079
2080 **Figure 5: The potential bi-directional relationship between obstructive sleep apnoea and**
2081 **Hyperaldosteronism and the plausible linking mechanisms.** IH: Intermittent hypoxia; RAAS:
2082 Renin-angiotensin-aldosterone system; RH: resistant hypertension; PA: primary aldosteronism;
2083 MR: mineralocorticoid receptors.

2084
2085 In rodent studies, IH promoted angiotensin I and AT1 expression, increased the activation of the
2086 carotid body by Angiotensin II and resulted in increased renin and aldosterone levels leading to
2087 increased BP^{169, 170, 159}. In addition, oxidative stress has been shown to increase the activation of the
2088 mineralocorticoid receptors (MR) in rodent models¹⁷¹. Whether OSA is associated with renin
2089 activations remains to be explored by further better designed studies of larger sample size as the
2090 current studies show a non-significant trend.

2091 The plausible mechanisms for the increased risk of OSA in patients with hyperaldosteronism are is
2092 plausible due to the increased sodium and fluid retention resulting in UA oedema, increased UA
2093 resistance and collapse^{159, 176-178}. This might have been worsened further by increases in neck
2094 circumference and oedema due to fluid displacement during recumbency overnight particularly in
2095 patients with RH^{159, 178}, which is supported by a study showing a reduction in neck circumference with
2096 improvements in AHI after treatment of PA with either MR antagonist or adrenalectomy¹⁷².

2097
2098 **Figure 6: OSA & HPA axis dysregulation A.** Possible underlying mechanisms linking OSA to
2099 HPA axis dysregulation **B.** Possible mechanisms linking hypercortisolism with OSA development
2100 CRH: Corticotropin Releasing Hormone, ACTH: Adrenocorticotrophic hormone

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Figure 7: OSA & GH/IGF axis. A. Possible underlying mechanisms for OSA leading to GH/IGF axis dysregulation. B. Possible mechanisms linking GH excess (red arrows) and GH deficiency (blue arrows) with OSA development.

The main causal mechanisms linking acromegaly to OSA are related to the anatomical changes that occur as a result of GH excess leading to narrower and more collapsible UAs. Patients with acromegaly have vertical growth of the mandible, which leads to pharyngeal obstruction due to the retroposition of the tongue base with caudal displacement of the hyoid²²⁵. In addition, soft tissue thickening/swelling, secondary to increased glycosaminoglycan deposition, collagen and tissue oedema, and macroglossia contribute to the compromise of UAs in patients with acromegaly²²⁶⁻²³⁴. This is supported by a study using MRI and nasopharyngoscopy that showed the tongue base and uvula to be the main site of UA obstruction in patients with OSA and acromegaly²¹⁶. In addition, the uvula diameter correlated to the severity of the UA collapse and tongue measurements correlated to the AHI and IGF-1 levels^{216, 230}. The weakness of UA muscles (sternohyoid muscle) also contributes to the increased risk of UA collapsibility in patients with acromegaly²³⁵. Other factors include hypothyroidism, large goiters (detailed later)^{219, 236, 237}, insulin resistance and dysglycaemia^{219, 224, 238}.

Figure 8: Mechanisms linking OSA and Hypothyroidism

Hypothyroidism can lead to increased UA collapsibility due to soft tissue swelling (in tongue, neck, and pharynx) caused by mucopolysaccharides infiltration (myxoedema in the more severe form)²⁵⁶. In support of this mechanism, LT4 treatment reduced soft tissue swelling and improved AHI, nocturnal hypoxaemia and sleep architecture in an uncontrolled study²⁵⁴. Goitre (regardless of thyroid status) can cause UA obstruction and collapse^{256, 263}. It causes narrowing of the UA by direct mechanical obstruction, especially in supine position, and by increasing laryngeal oedema due to reduced venous return; both of which can be resolved following thyroidectomy or LT4 in some cases^{256, 264-266}. Hypothyroidism (especially when severe) can also result in blunted ventilatory drive and impaired chemosensors' response to hypoxia/ hypercapnia in animal and human studies²⁵⁶. This is possibly due to decreased dopamine receptor (D1) expression in the brain stem and the CB in rodents with hypothyroidism²⁶⁷, and can be reversed with LT4 treatment²⁵⁶. Impaired UA dilator muscle function in hypothyroidism, due to altered myosin heavy chain expression in rodent studies and neuropathy in humans, has also been reported^{217, 268}. Furthermore, the diaphragm has been shown to be weaker in rodents and human studies in hypothyroidism, which

2133 result in a reduction in lung volumes contributing to OSA development/worsening^{253, 256, 269}. The
2134 diaphragm weakness can be improved by LT4 treatment²⁵³. Finally, obesity could be potentially
2135 another link between OH and OSA as studies have shown that patients with OH are about 5-7kg
2136 heavier compared to euthyroid matched-controlled²⁷⁰. However, this weight-increase in OH seems to
2137 be related to expanded water compartment rather than fat mass. In addition, LT4 treatment causes
2138 weight loss by reducing lean mass rather than fat mass (based on DXA)^{271, 272}.

2141 **Figure 9: Obstructive Sleep Apnoea and Polycystic Ovary Syndrome; clinical interactions**
2142 **and underlying pathophysiology.** Adapted from Kahal et al. with permission.

2143 Sex hormones are thought to play a role in this bidirectional relationship, as in women with PCOS
2144 androgens excess along with lower progesterone (as a result of anovulation) can increase UA
2145 collapsibility and/ or lead to blunted ventilator chemo-responsiveness³²². While, IH and sleep
2146 fragmentation can impact HPG axis and can influence GnRH and gonadotropins pulsatility, leading to
2147 causing/ or worsening PCOS phenotype³²². In addition, IR and dysglycemia in women with PCOS can
2148 contribute to worsening or the development of OSA;³²². Obesity is common in both disorders and can
2149 contribute to the associations between OSA and PCOS. Other common comorbidities are oxidative
2150 stress, endothelial dysfunction and sympathetic activation all of which can lead to a vicious cycle of
2151 OSA and PCOS entities³²².

2153 **Figure 10: OSA & Bone metabolism.**

2154 GH: Growth hormone, PTH: Parathormone, BMD: Bone mineral density, BRMs: Bone Resorption
2155 Markers

2156 As with other endocrine consequences of OSA, hypoxaemia plays an important role as has been
2157 shown by Cauley et al and IH in human cell cultures and rodents can increase osteoclasts and inhibit
2158 osteoblasts' growth and differentiation via HIF transcription factor family (HIF-1a and HIF-2a) and
2159 VEGF³³³⁻³³⁷. In addition, IH can result in increased inflammation and oxidative stress that can lead to
2160 higher risk of osteoporosis and fractures³³⁸⁻³⁴⁰. Other mechanisms including hyperleptinaemia and
2161 sympathetic activation increase bone resorption and inhibit bone formation leading to bone mass
2162 loss^{341, 342}. Changes in melatonin profile could also contribute to the impact of OSA on bones, as
2163 patients with OSA might have changed melatonin profile and lower melatonin serum levels compared
2164 to people without OSA due to frequent nocturnal awakening and light exposure³⁴³. Melatonin has

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2165 been shown to increase bone mass density in a RCT³⁴⁴. Furthermore, serum 25-hydroxyvitamin D was
2166 found to be lower (: 19.34 ± 9.54 ng/ml vs. 32.83 ± 16.93 ng/ml, p < 0.0001) and PTH levels higher (:
2167 62.57 ± 29.97 pg/mL vs. 40.05 ± 31.12 pg/mL, p < 0.0001) in patients with OSA compared to healthy
2168 controls³⁴⁵. CPAP for 7 nights increased 25-hydroxyvitamin D concentrations (19.21 ± 9.45 vs. 21.03 ±
2169 9.50, F = 8.32, p < 0.01) but had no effect on PTH³⁴⁵. The suppression of the gonadal axis and GH in
2170 OSA and the associated insulin resistance could also contribute to the impact of OSA on bone
2171 metabolism³⁴². T2D in particular can have detrimental effects on bone mass and fracture risk³⁷⁴⁻³⁷⁷
2172 and as OSA increases the risk of T2D, then T2D is a potential mechanism between OSA and bone
2173 disease.
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Figure 1

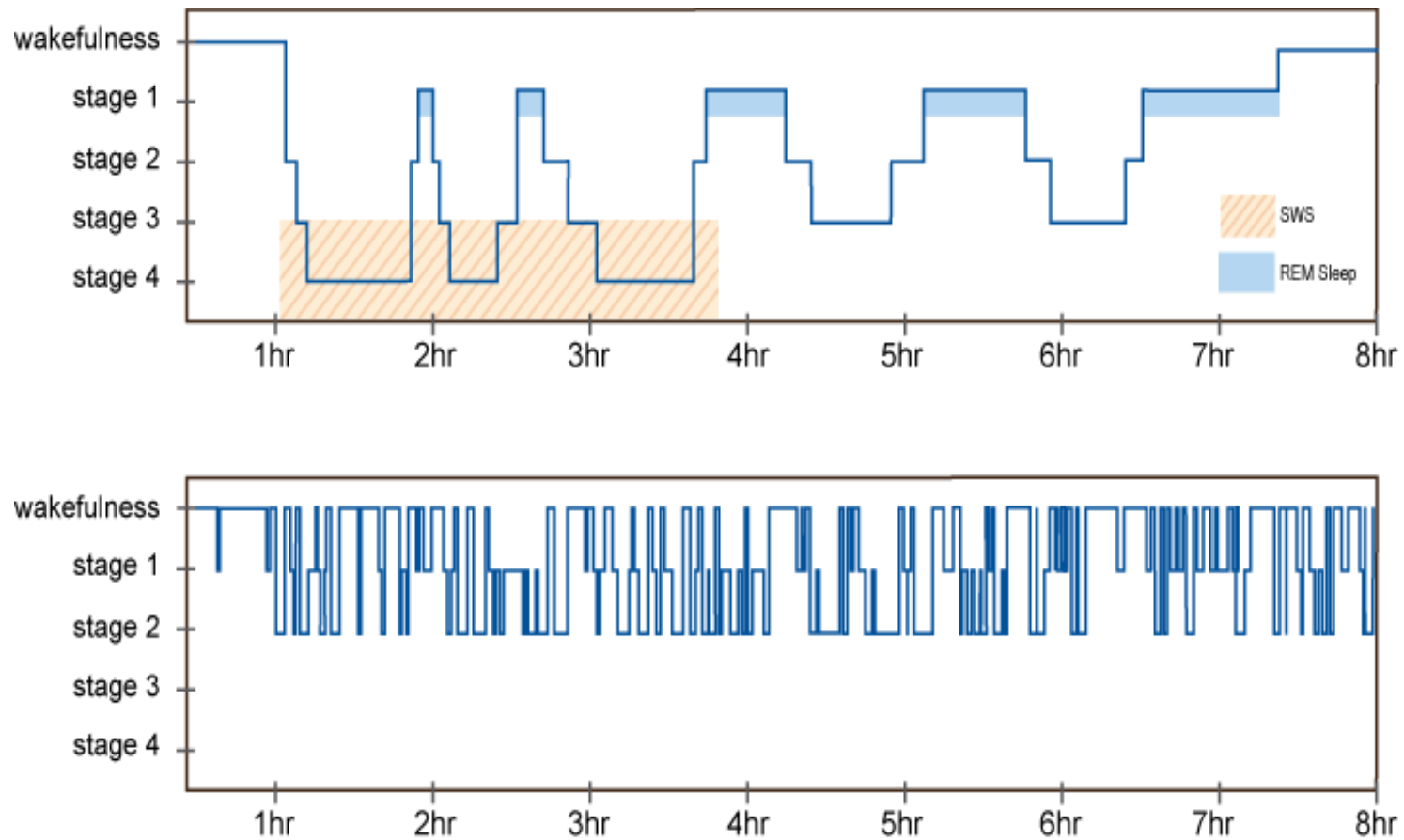


Figure 2

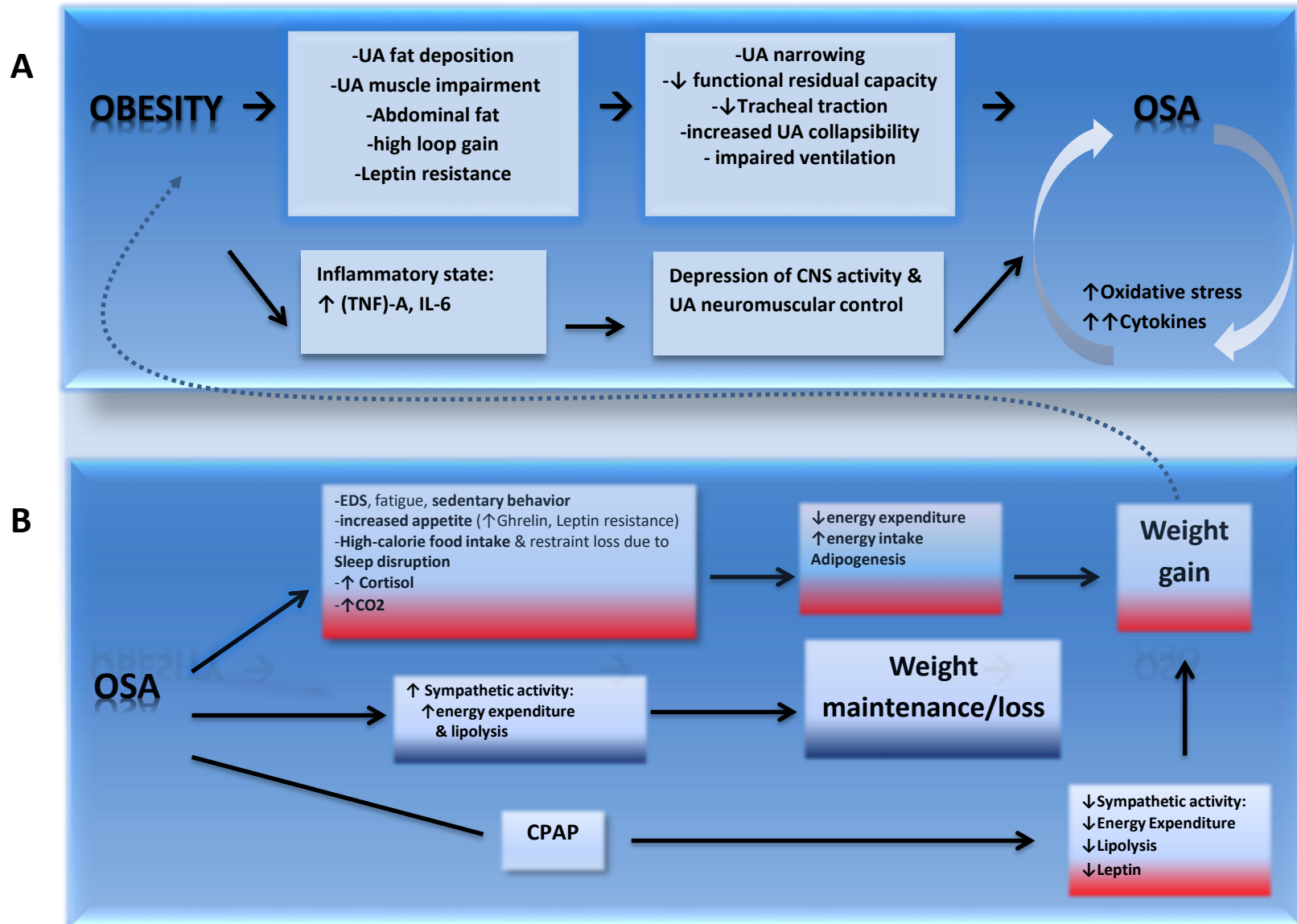


Figure 3

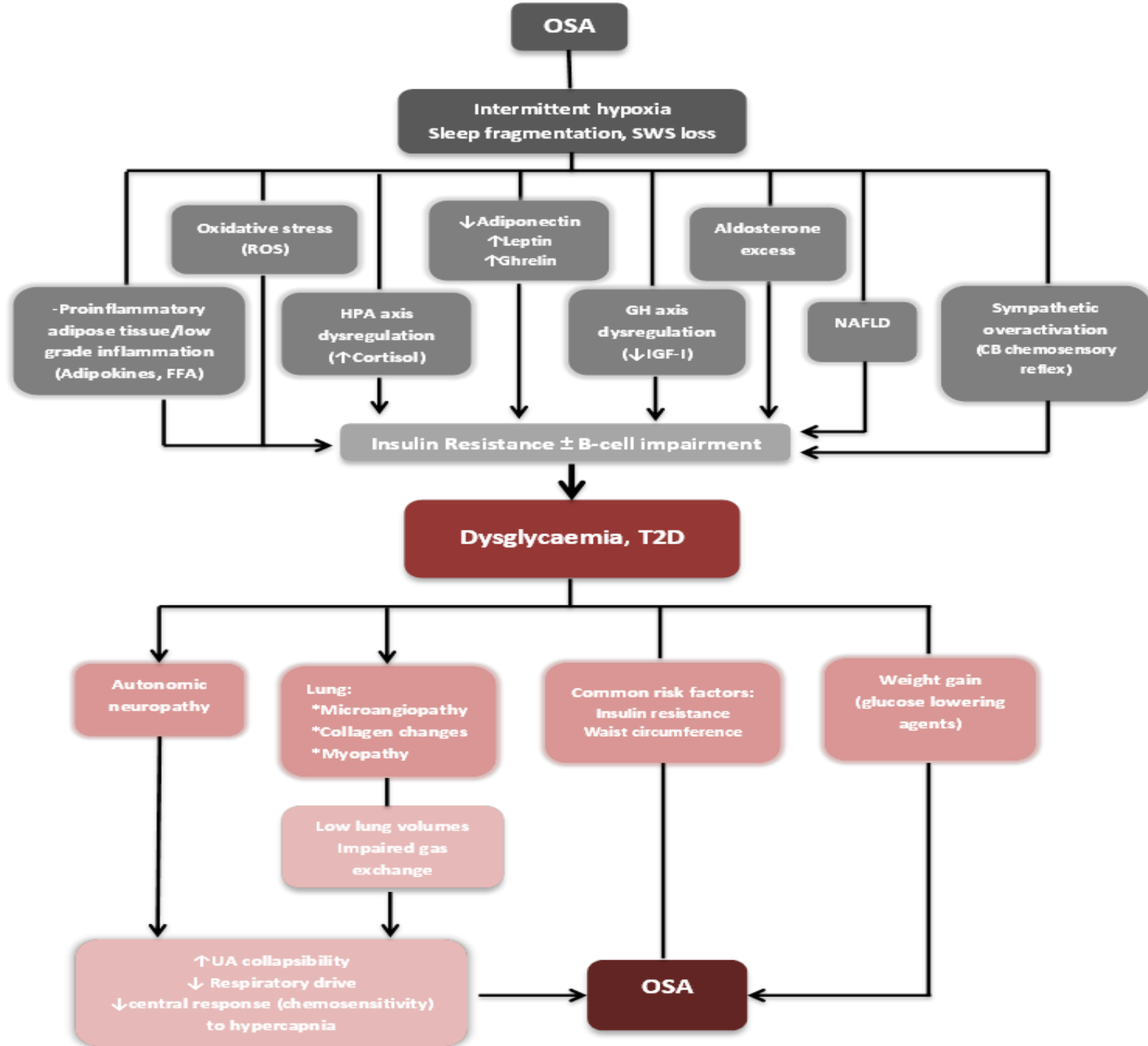


Figure 4. A

REF: Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. [Jullian-Desayes I](#), [Joyeux-Faure M](#), [Tamisier R](#), [Launois S](#), [Borel AL](#), [Levy P](#), [Pepin JL](#). [Sleep Med Rev](#). 2015 Jun;21:23-38. doi: 10.1016/j.smrv.2014.07.004. Epub 2014 Jul 31. **(Permission needed)**

Figure 4. B

REF: Obstructive Sleep Apnoea and Type 2 Diabetes. Abd A Tahrani¹ and Asad Ali². *European Endocrinology*, 2014;10(1):43–50 **(Permission needed)**

Figure 4

A.

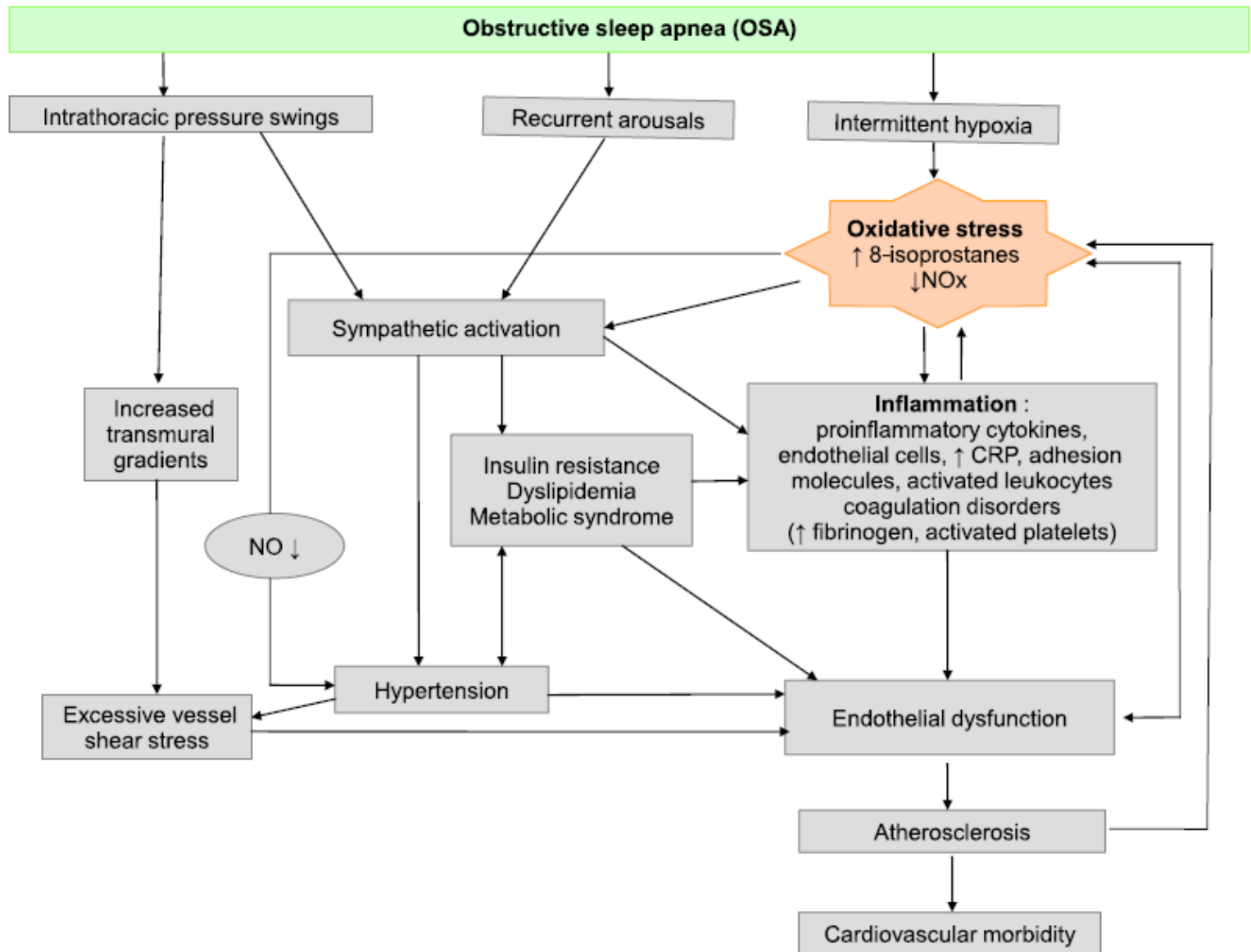


Figure 4

B.

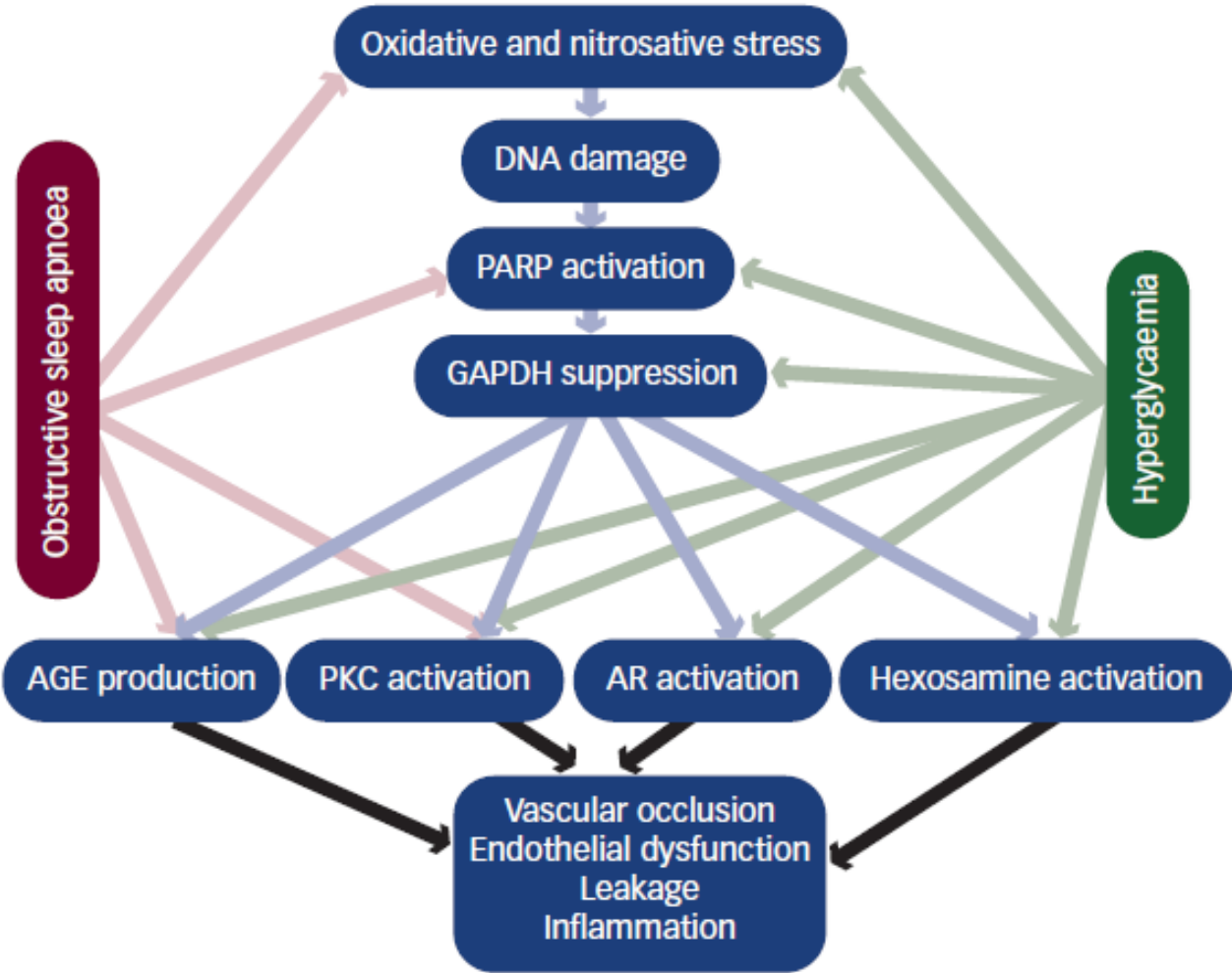


Figure 5

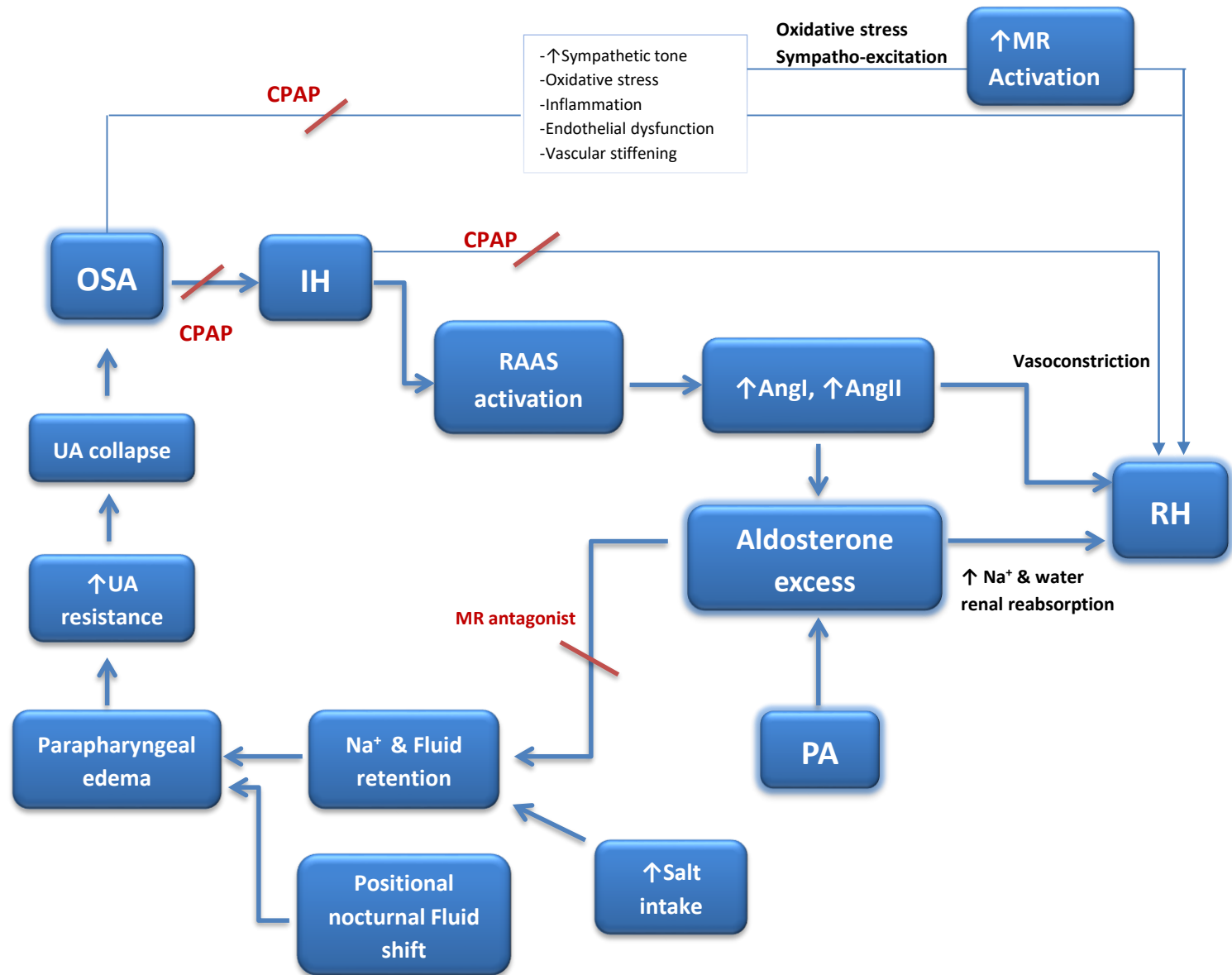


Figure 6

A.

Obststructive
Sleep
Apnoea

- Night awakenings
- Sleep restriction
- Intermittent hypoxia
- Autonomic activation



- ↑**CRH** release
- ↑**ACTH** responsiveness
- ↑ pulsatile **cortisol** release

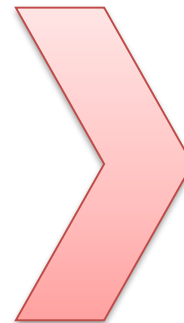


HPA
Axis (**up**)
dysregulation

B.

Hypercortisolism
(Cushing's s.)

- Obesity
- Hyperglycaemia
- UA fat deposition
- UA myopathy



OSA

Figure 7

A.



B.

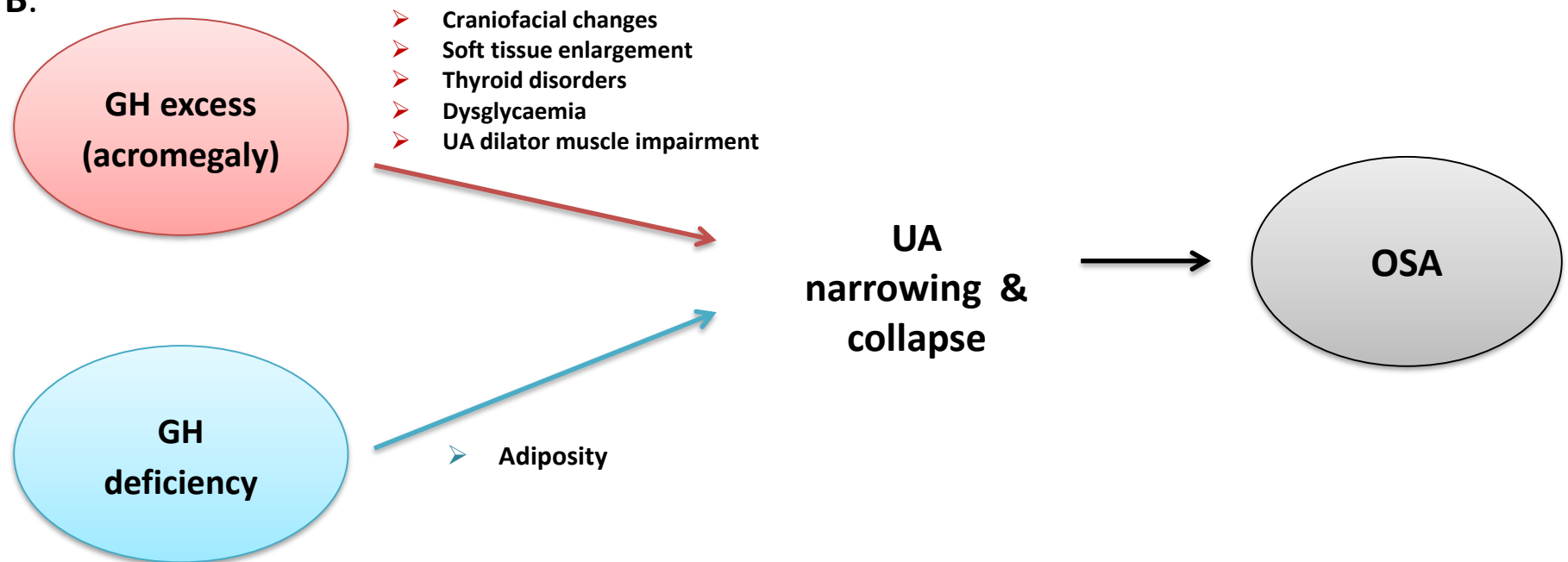


Figure 8

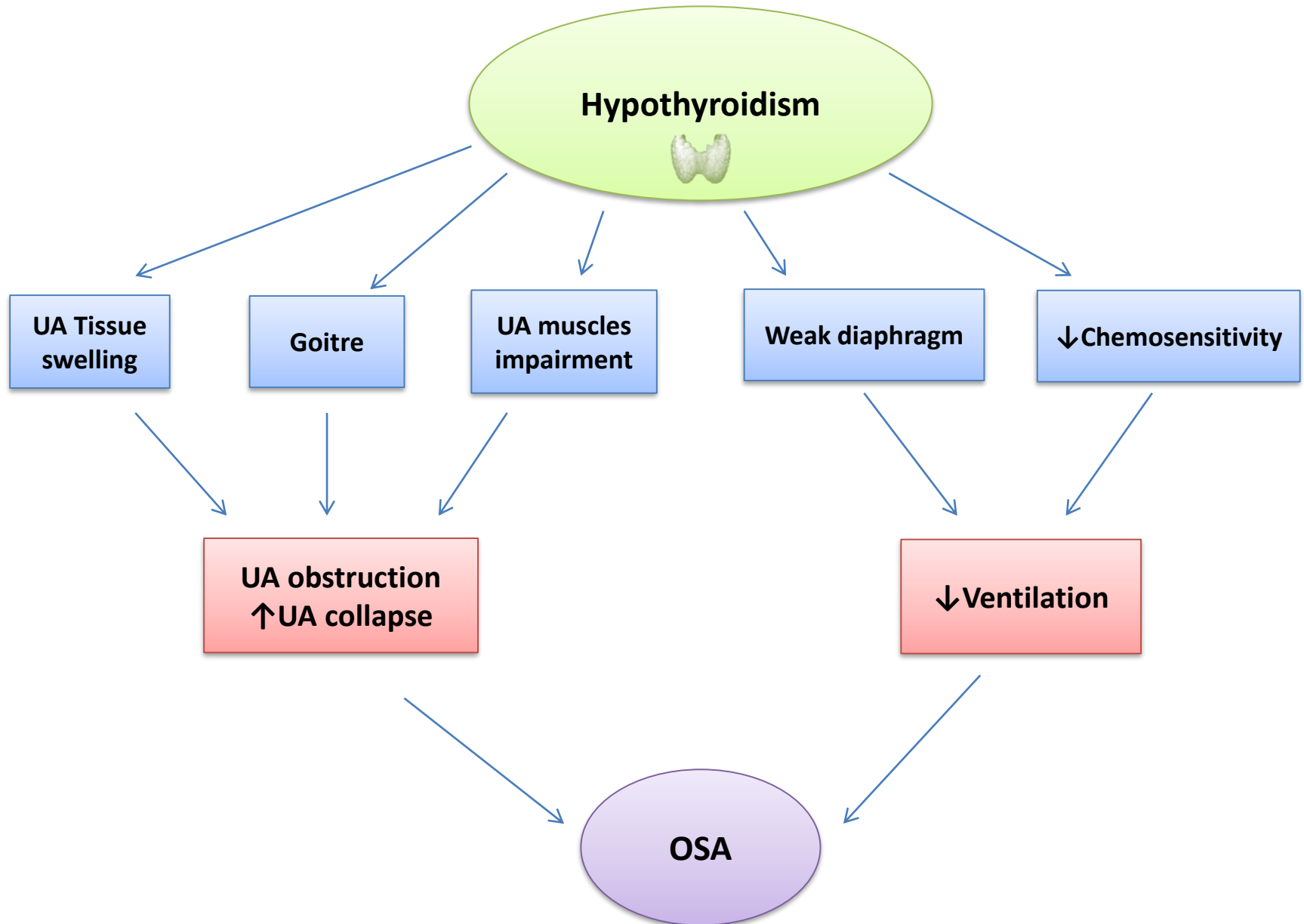
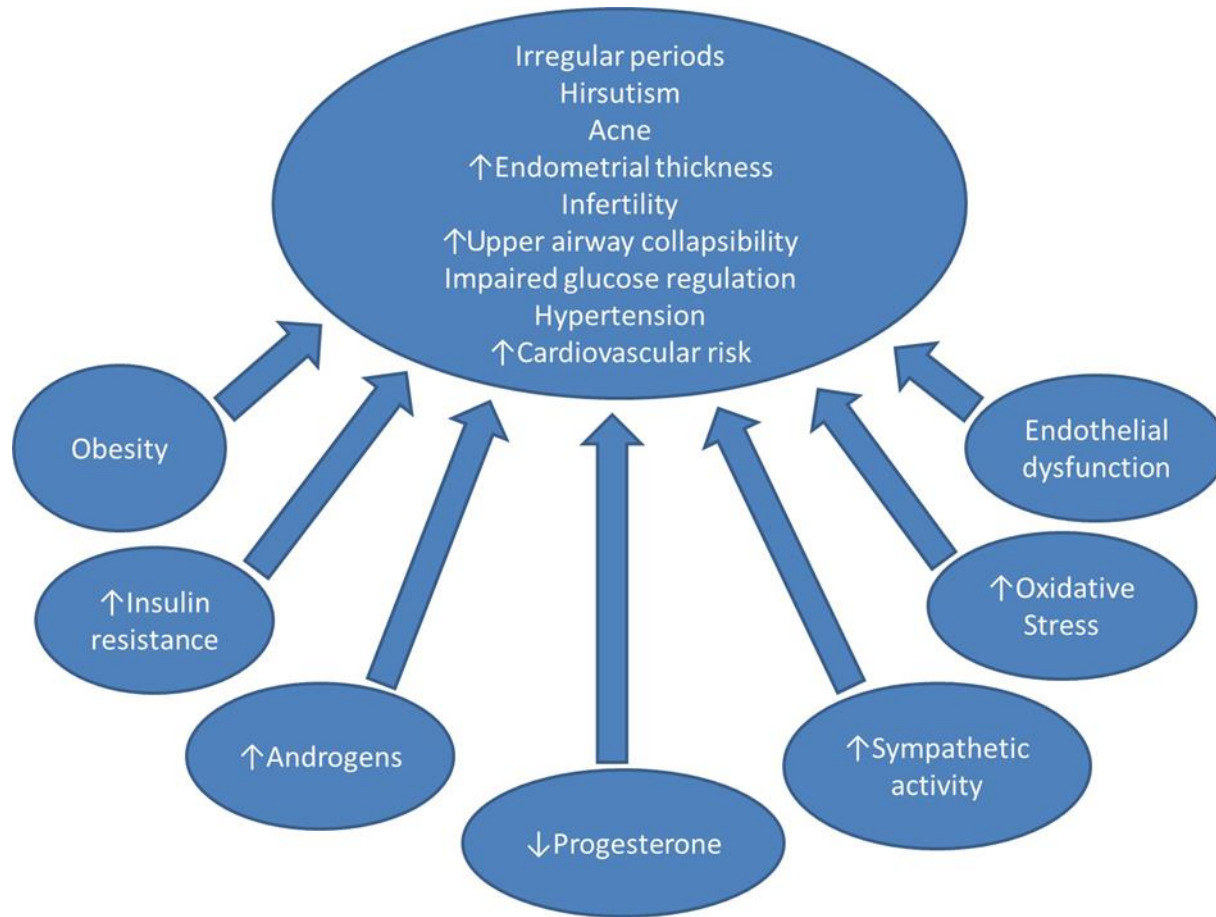
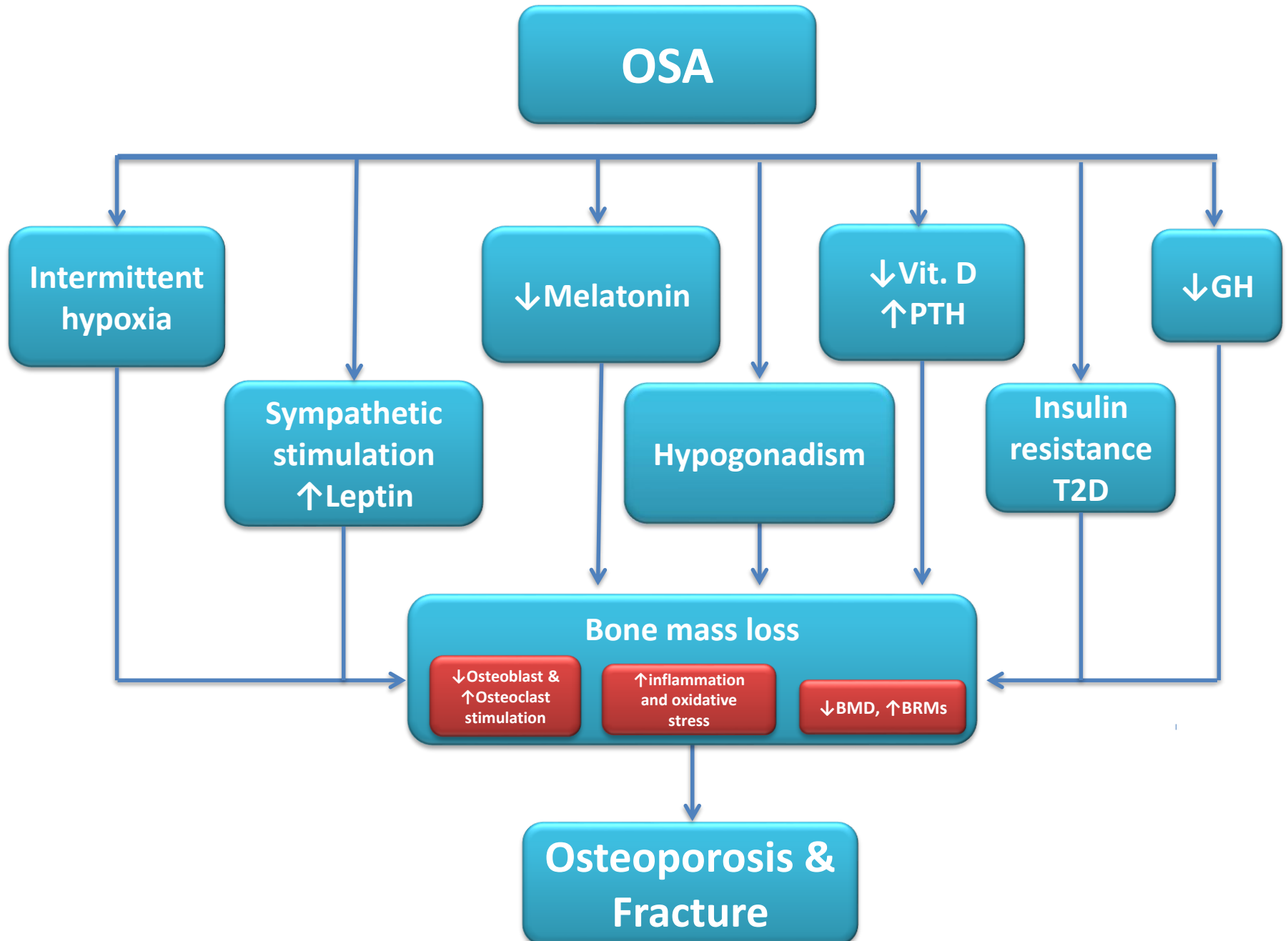


Figure 9



Ref: Hassan Kahal, Ioannis Kyrou, Abd A. Tahrani, Harpal S. Randeva . Obstructive sleep apnoea and polycystic ovary syndrome: A comprehensive review of clinical interactions and underlying pathophysiology. [Clin Endocrinol \(Oxf\)](#). 2017 Oct;87(4):313-319. doi: 10.1111/cen.13392. Epub 2017 Jul 14. **(Permission needed)**

Figure 10



Online Supplement

OSA overview

OSA pathogenesis

Although the upper airway (UA) consists of rigid, cartilaginous structures, its patency can be compromised along a soft segment extending from the hard palate to the larynx (the pharynx), which allows the UA to change shape for speech and swallowing during wakefulness¹⁻³. However, in the presence of anatomically compromised upper airways (UAs), as in patients with OSA, the loss of wakefulness inputs to the control of the UAs and chest wall muscle motor neurons during sleep, produce UAs obstruction⁴. The underlying mechanisms driving these UAs obstructions are complex and multi factorial (**Figure 1 of the online supplement**).

Patients with OSA have narrower UAs^{5,6} with enlarged surrounding soft tissues compared to healthy controls; thus increasing the risk of collapse during sleep (**Figure 2 of the online supplement**)⁷⁻¹¹. During wakefulness, the UA dilator muscles (genioglossus most studied) activity is increased in patients with OSA, compared to healthy controls, compensating for the anatomically diminished UA size; while during sleep the UA dilator muscles activity is greatly reduced leading to pharynx collapse and subsequently UA obstruction, particularly during rapid-eye-movement (REM) sleep^{1, 2, 12, 13}. This reduction in UAs muscle tone during sleep is due to a combination of central lack of respiratory drive and local inhibitory reflexes that respond to changes in pressure in the UAs¹. The chemoreceptors are also less responsive to PaO₂ and PaCO₂ changes during sleep¹⁴, resulting in a reduced input to the respiratory centers in the brainstem and reduced UA dilators activity¹⁵⁻¹⁷. Even very small and transient reductions in PaCO₂ can result in significant apnoea due to the changes in chemoreceptors activity during sleep⁴. The reduced UA dilator muscles activity is also due to reduced mechanoreceptors' responses to changes in negative UA pressure (genioglossus negative pressure reflex^{18, 19}) during REM.

Respiratory arousal threshold (RAT) also plays an important role in the pathogenesis of OSA in some patients²⁰. In response to changes in gas exchange, pH, lung volumes or UAs resistance, the respiratory centres in the brainstem can increase respiratory effort, which triggers an arousal from sleep when RAT is reached^{2, 21}. Hence, arousals are protective as they increase UA muscle tone (similar to the awake state) and finally open obstructed UAs¹. However, low RAT can have detrimental effects in patients with OSA as more frequent

arousals can result in a disruption in sleep architecture and in restoring airflow before the development of adequate ventilatory drive and result in ventilatory overshoot associated with the sleep/wake transition leading to further obstructive episodes^{1, 2, 20-23}.

Another important element in OSA development is the ventilatory control stability, known as loop gain, which refers to the size of a “ventilatory correction” as a response to a “ventilatory disturbance”^{2, 24}. Accordingly, in case of a high loop gain, small decrease in breathing will lead to a large correction. In the case of OSA, the loop gain appears to be elevated²⁵, suggesting high responsiveness of the ventilatory system to disturbed breathing with a propensity to develop cyclical fluctuations in breathing output and increased response to arousal by hyperventilation driving PaCO₂ below the apnea threshold^{1, 26, 27}.

There are multiple other factors that contribute further to the pathogenesis of OSA and UA collapsibility including low lung volume (resulting in lack of pharyngeal stretching), reduced UAs surface tension and UA oedema^{2, 28-32}.

OSA risk factors

Excess body weight is the main risk factor for OSA³³. Weight gain of 10% is associated with a 6-fold higher risk of moderate to severe OSA development³⁴. Similarly, 9% weight loss in patients with obesity and OSA results in 47% reduction in apneas frequency³⁵ and 60% reduction in the Apnoea- Hypopnoea index (AHI) after 17% drop in BMI³⁶. Men have consistently been shown to be at a 2- to 3-fold higher risk of OSA compared to women³⁷; possibly due to differences in sex hormones which will be detailed later. Multiple studies showed African-Americans to be at increased risk of OSA compared to White Caucasians³⁸⁻⁴⁰. Whereas, differences in the prevalence of OSA in Asians vs. white Caucasians were inconsistent across multiple studies^{38, 41, 42}. The ethnic variations could be related to differences in UA anatomy, respiratory arousal thresholds, fat distribution, genetic and environmental factors^{37, 43-45}. Prevalence of OSA increases with increasing age³³, being 2-3 fold higher in older people (≥65y), reaching eventually a plateau after the age of 65³⁷. Other risk factors include smoking, excess alcohol intake, nasal obstruction and menopause³⁷.

OSA clinical features

Snoring is the most frequent OSA symptom symptom but it is not diagnostic for the disease, as most snorers don't have OSA and; only 6% of patients with OSA do not report snoring⁴⁶, but it is very frequent in general population as well⁴⁶. Other clinical features include, witnessed apneas, nightly choking and gasping (reflecting an arousal after an apnea event), insomnia, nocturia, enuresis, arousals, sweating⁴⁷, excessive daytime sleepiness (EDS), and a

variety of other daytime symptoms such as fatigue, memory loss, irritability, morning headaches, depression, and erectile dysfunction^{46, 48}.

OSA comorbidities and associations:

OSA is associated with significant comorbidities such as hypertension, Type 2 diabetes, cardiovascular disease, mortality, road traffic accidents, chronic kidney disease amongst others^{4, 47, 49, 50}.

OSA diagnosis and treatment:

Multiple definitions of OSA have been used in clinical research, which contributed to some of the variations in outcomes of studies in patients with OSA. OSA is generally diagnosed based on cut offs of parameters recorded during polysomnography or polygraphy. The AHI is defined as the average number of apnoea and hypopnea events per hour of sleep. The respiratory disturbance index (RDI) is defined as the AHI plus the respiratory-effort related arousals. The oxygen desaturation index (ODI) is the average number of oxygen desaturation per hour of sleep. The American Academy of Sleep Medicine (AASM) recommendations regarding OSA diagnosis and the criteria used to define apnoea and hypopneas are detailed here^{51, 52}.

Polysomnography remains the gold-standard for diagnosing OSA, although multiple portable devices have also been considered appropriate if adequate channels are recorded according to the latest AASM guidelines⁵². Sleep staging is desirable but not always considered essential. CPAP is the gold standard treatment for patients with moderate to severe OSA in addition to weight loss in patients with obesity^{48, 53, 54}. Intra oral devices can be used in mild OSA and more recently upper airway stimulation can also be used in certain patients groups^{55, 56}.

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Figures for the online supplement

Figure 1: Summary of the pathogenesis of obstructive sleep apnoea (OSA). P_{crit} : Critical closing pressure (The pressure inside the airway at which the airway collapses); $PaCO_2$: Partial pressure of Carbon dioxide in arterial blood

Ref: Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of Sleep Apnea. *Physiol Rev* 90: 47–112, 2010; doi:10.1152/physrev.00043.2008 (**Permission needed**)

Figure 2: Upper airways size in patients with OSA and healthy individuals (top); and the impact of sleep on upper airways size in a healthy individual (bottom).

A: midsagittal magnetic resonance image (MRI) in a normal subject (left) and in a patient with severe OSA (right). Highlighted are the four upper airway regions (nasopharynx, retropalatal region, retroglossal region, hypopharynx) and upper airway soft tissue (soft palate, tongue, fat) and craniofacial structures (mandible). Fat deposits are shown in white on the MRI. Note that in the apneic patient: a) the upper airway is smaller, in both the retropalatal and retroglossal region; b) the soft palate is longer and tongue size is larger; and c) the quantity of subcutaneous fat is greater. **B:** state dependence of upper airway size in a normal subject as assessed via three-dimensional reconstructions of MRI images. Images represent averages taken over several respiratory cycles during eupneic breathing in sleep and wakefulness. Airway volume during NREM sleep is smaller in the retropalatal (RP) region, not in the retroglossal (RG) region. Such images show the marked effect of sleep, per se, on the loss of upper airway muscle dilator tone and also show that the upper airway does not narrow as a homogeneous tube during sleep.

Ref: Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of Sleep Apnea. *Physiol Rev* 90: 47–112, 2010; doi:10.1152/physrev.00043.2008 (**Permission needed**)

Figure 1

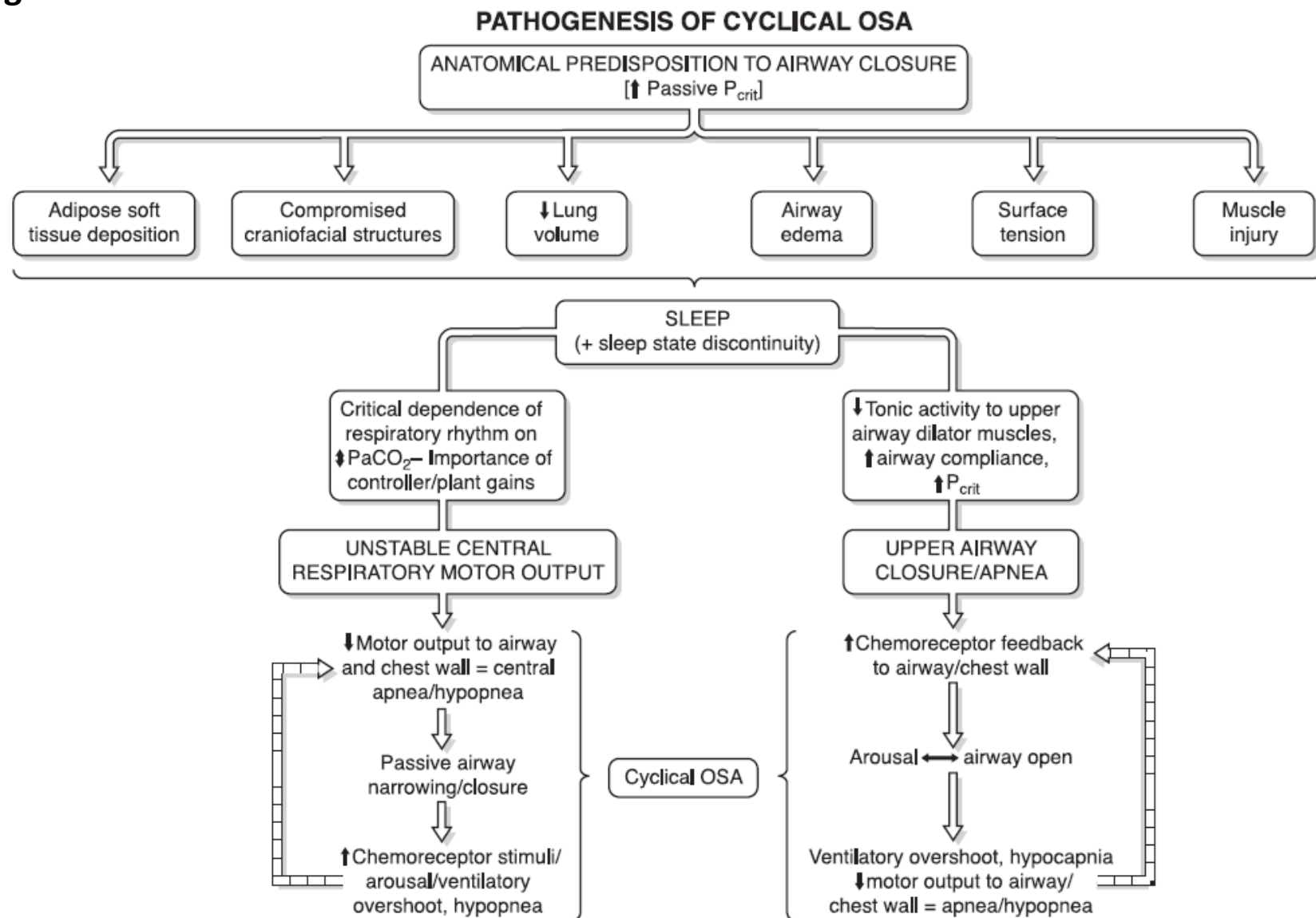


Figure 2

